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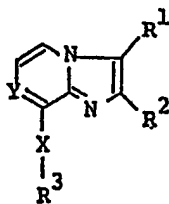
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(54) Imidazoheterocyclic compounds processes for preparation thereof and pharmaceutical compositions comprising them.

(57) Imidazoheterocyclic compounds of the formula:



wherein R¹ is lower alkenyl, lower alkynyl, lower alkadienyl,
 lower alkenyloxy (lower) alkyl, lower alkynyloxy(lower)alkyl,
 carboxy(lower)alkynyloxy(lower)alkyl or protected carboxy-
 (lower)alkynyloxy(lower)alkyl,

R² is hydrogen, lower alkyl or aryl,

R³ is ar(lower)alkyl which may have one or more suitable
 substituent(s), ar(lower)alkenyl, condensed bicyclic hydro-
 carbon group, lower alkyl having cyclo(lower)alkyl or lower
 alkyl,

X is O or NH, and

Y is CH or N

and a pharmaceutical acceptable salt thereof, processes for
 their preparation and pharmaceutical compositions compris-
 ing them as an active ingredient.

IMIDAZOHETEROCYCLIC COMPOUNDS
PROCESSES FOR PREPARATION THEREOF
AND PHARMACEUTICAL COMPOSITIONS COMPRISING THEM

— The present invention relates to novel imidazoheterocyclic compounds and pharmaceutically acceptable salt thereof. More particularly, it relates to novel imidazoheterocyclic compounds and
5 pharmaceutically acceptable salts thereof which have antiulcerative activity, to processes for preparation thereof, to a pharmaceutical composition comprising the same, and to a method of using the same therapeutically in the treatment of ulcer in human or animals.

10 Accordingly, one object of the present invention is to provide novel imidazoheterocyclic compounds and pharmaceutically acceptable salt thereof, which are useful as an antiulcerative agent.

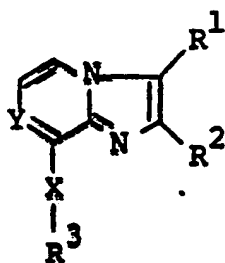
15 Another object of the present invention is to provide processes for preparation of said imidazoheterocyclic compounds and salts thereof.

A further object of the present invention is to provide a pharmaceutical composition comprising,

as an active ingredient, said imidazoheterocyclic compound or its pharmaceutically acceptable salt.

Still further object of the present invention is to provide a method of using said imidazoheterocyclic compound or its pharmaceutically acceptable salt in the treatment of ulcer in human or animals.

The imidazoheterocyclic compounds of the present invention are novel and can be represented by the formula (I) :



(I)

wherein R^1 is lower alkenyl, lower alkynyl, lower alkadienyl, lower alkenyloxy(lower)alkyl, lower alkynyloxy(lower)alkyl, carboxy(lower)alkynyloxy(lower)alkyl or protected carboxy(lower)alkynyloxy(lower)alkyl;

R^2 is hydrogen, lower alkyl or aryl,

R^3 is ar(lower)alkyl which may have one or more suitable substituent(s),

ar(lower)alkenyl, condensed bicyclic hydrocarbon group, lower alkyl having cyclo(lower)alkyl or lower alkyl,

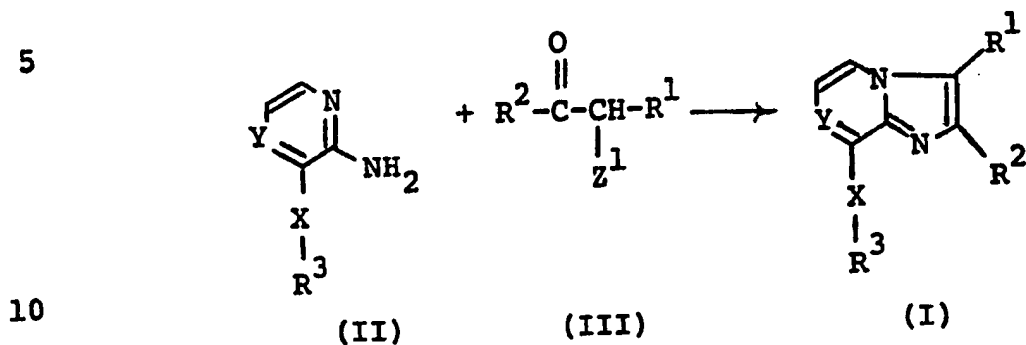
X is O or NH, and

Y is CH or N.

According to the present invention, the object

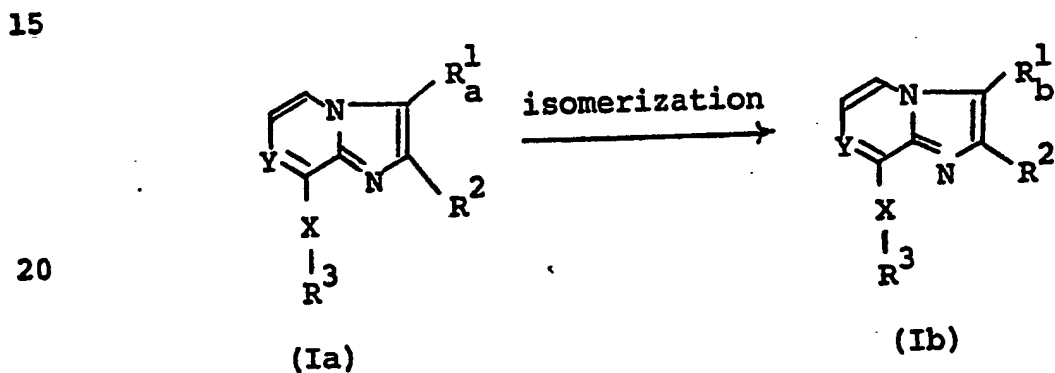
compounds (I) can be prepared by the following processes.

Process 1



or a salt thereof or a salt thereof or a salt thereof

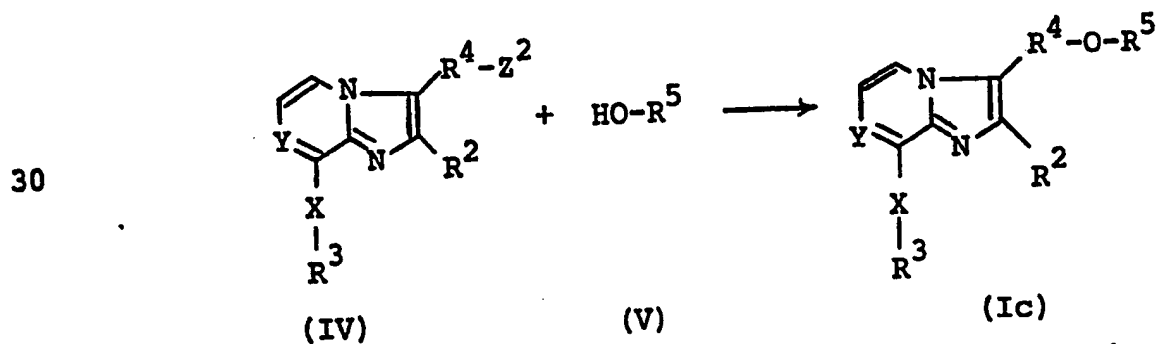
Process 2



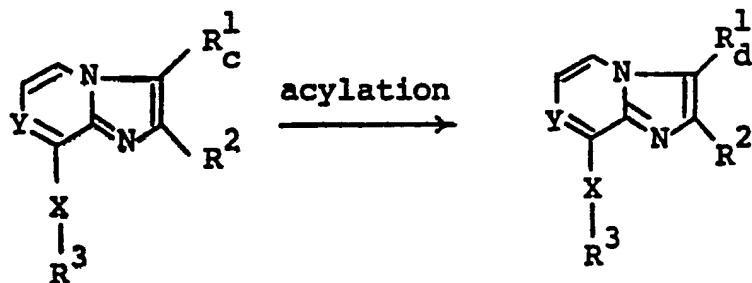
or a salt thereof

or a salt thereof

Process 3



or a salt thereof or a salt thereof or a salt thereof

Process 4

(Id)

(Ie)

or a salt thereof

or a salt thereof

wherein R^1 , R^2 , R^3 , X and Y are each as defined above,

R_a^1 is lower alkynyl,

R_b^1 is cumulated lower alkadienyl,

R_c^1 is (ω -lower alkynyloxy) (lower)alkyl,

R_d^1 is (ω -carboxy- ω -lower alkynyloxy) (lower)alkyl
or (ω -protected carboxy- ω -lower alkynyloxy)-
(lower)alkyl,

R^4 is lower alkylene,

R^5 is lower alkenyl, lower alkynyl,

carboxy(lower)alkynyl or

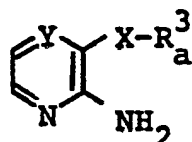
protected carboxy(lower)alkynyl,

Z^1 is an acid residue, and

Z^2 is a leaving group.

As to the starting compounds (II), (III) and (IV), some of them are novel and can be prepared by the procedures disclosed in the Preparations as mentioned later.

Especially, some of said novel starting compound (II) can be represented by the following general formula :



(VI)

wherein R_a^3 is lower alkyl having cyclo(lower)alkyl or ar(lower)alkyl which may have one or more substituent(s),

X is O or NH, and

Y is CH or N,

provided that when X is O and Y is CH,

then R_a^3 is lower alkyl having cyclo(lower)alkyl.

Suitable pharmaceutically acceptable salts of the object compounds (I) are conventional non-toxic salts and include a salt with a base or an acid addition salt such as a salt with an inorganic base, for example, an alkali metal salt (e.g. sodium salt, potassium salt, etc.), an alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.), an ammonium salt; a salt with an organic base, for example, an organic amine salt (e.g. triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.) etc.; an organic acid addition salt (e.g. acetate, maleate, tartrate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate, etc.), an inorganic acid addition salt (e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.), a salt with an amino acid (e.g. arginine, aspartic acid, glutamic acid, etc.), and the like.

In the above and subsequent descriptions of the present specification, suitable examples and illustrations of the various definitions which the present invention includes within the scope thereof are explained in detail as follows.

The term "lower" is intended to mean 1 to 6 carbon atom(s), unless otherwise indicated.

Suitable "lower alkyl" may be the ones having 1 to 6 carbon atom(s) and may include methyl, ethyl, propyl,

isopropyl, n-butyl, t-butyl, pentyl, hexyl, and the like, in which the preferred one may be C_1 - C_4 alkyl and the more preferred one may be methyl and ethyl.

5 Suitable "lower alkenyl" may be the ones having 2 to 6 carbon atoms and may include vinyl, allyl, isopropenyl, 1(or 2 or 3)-butenyl, 1(or 2 or 3 or 4)-pentenyl, 1(or 2 or 3 or 4 or 5)-hexenyl, and the like, in which the preferred one may be C_2 - C_4 alkenyl and the more preferred one may be allyl.

10 Suitable "lower alkynyl" may be the ones having 2 to 6 carbon atoms and may include ethynyl, 1(or 2)-propynyl, 1(or 2 or 3)-butynyl, 1-methyl-2-propynyl, 1(or 2 or 3 or 4)-pentynyl, 1(or 2 or 3 or 4 or 5)-hexynyl, and the like, in which the preferred one may be C_2 - C_4 alkynyl and the more preferred one may be 2-propynyl.

15 Suitable "lower alkadienyl" may be the ones having 3 to 6 carbon atoms and may include 1,2-propadienyl, 1,2-butadienyl, 1,3-butadienyl, 2,3-pentadienyl, 1,4-pentadienyl, 1,2-hexadienyl, 1,3-hexadienyl, 1,4-hexadienyl, and the like, in which the preferred one may be C_3 - C_5 alkadienyl and the more preferred one may be 1,2-propadienyl.

25 (to be continued to the next page)

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35

"Cumulated lower alkadienyl" means the above-defined "lower alkadienyl" group in which two double bonds are adjacent to each other through one carbon atom, and suitable examples of such "cumulated lower alkadienyl" may include 1,2-propadienyl, 1,2-butadienyl, 2,3-pentadienyl, 1,2-hexadienyl, and the like, in which the preferred one may be cumulated C_3 - C_5 alkadienyl and the more preferred one may be 1,2-propadienyl.

In the term "lower alkenyloxy(lower)alkyl", suitable "lower alkenyl" moiety and "(lower)alkyl" moiety can be referred to the ones as mentioned above, respectively, and suitable examples of such "lower alkenyloxy(lower)alkyl" may include vinyloxymethyl, allyloxymethyl, 1-allyloxyethyl, 1-allyloxypropyl, 3-allyloxybutyl, 3-(2-butenyloxy)butyl, 5-(3-pentenyl)oxy)pentyl, 1-(2-hexenyloxy)hexyl, and the like, in which the preferred one may be (C_2-C_4) alkenyloxy(C_1-C_4)alkyl and the more preferred one may be allyloxymethyl.

In the term "lower alkynyloxy(lower)alkyl", suitable "lower alkynyl" moiety and "(lower)alkyl" moiety can be referred to the ones as mentioned above, respectively, and suitable examples of such "lower alkynyloxy(lower)alkyl" may include ethynyloxymethyl, 2-propynyloxymethyl, 2-(2-propynyloxy)ethyl, 1-(2-butyloxy)propyl, 1-(3-butyloxy)propyl, 2-(3-butyloxy)butyl, 3-(3-butyloxy)butyl, 4-(1-pentyloxy)pentyl, 4-(4-pentyloxy)pentyl, 5-(5-hexynyloxy)hexyl, 6-(5-hexynyloxy)hexyl, and the like, in which the preferred one may be (C_2-C_4) alkynyloxy(C_1-C_4)alkyl and the more preferred one may be 2-propynyloxymethyl.

"Carboxy(lower)alkynyloxy(lower)alkyl" means the above-defined lower alkynyloxy(lower)alkyl group which is substituted with carboxy, and suitable examples of

such "carboxy(lower)alkynyloxy(lower)alkyl" may include carboxyethynyloxymethyl, 3-carboxy-2-propynyloxymethyl, 1-carboxy-2-propynyloxymethyl, 2-(3-carboxy-2-propynyloxy)ethyl, 1-(1-carboxy-2-butynyloxy)propyl, 1-(4-carboxy-3-butynyloxy)propyl, 2-(4-carboxy-3-butynyloxy)butyl, 3-(4-carboxy-3-butynyloxy)butyl, 4-(3-carboxy-1-pentynyloxy)pentyl, 4-(5-carboxy-4-pentynyloxy)pentyl, 5-(1-carboxy-5-hexynyloxy)hexyl, 6-(6-carboxy-5-hexynyloxy)hexyl, and the like, in which the preferred one may be carboxy(C₂-C₄)alkynyloxy(C₁-C₄)-alkyl and the more preferred one may be 3-carboxy-2-propynyloxymethyl.

"Protected carboxy(lower)alkynyloxy(lower)alkyl" means the above-defined lower alkynyloxy(lower)alkyl group which is substituted with protected carboxy, and suitable "protected carboxy" may be an esterified carboxy or the like, and concrete examples of the ester moiety in said esterified carboxy may be the ones such as lower alkyl ester [e.g. methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, tert-butyl ester, pentyl ester, hexyl ester, 1-cyclopropylethyl ester, etc.] which may have suitable substituent(s), for example, lower alkanoyloxy-(lower)alkyl ester [e.g. acetoxymethyl ester, propionyloxymethyl ester, butyryloxymethyl ester, valeryloxymethyl ester, pivaloyloxymethyl ester, 1-acetoxyethyl ester, 1-propionyloxyethyl ester, pivaloyloxymethyl ester, 2-propionyloxyethyl ester, hexanoyloxymethyl ester, etc.], lower alkanesulfonyl-(lower)alkyl ester [e.g. 2-mesyloethyl ester, etc.] or mono (or di or tri)halo(lower)alkyl ester [e.g. 2-iodoethyl ester, 2,2,2-trichloroethyl ester, etc.]; lower alkenyl ester [e.g. vinyl ester, allyl ester, etc.]; lower alkynyl ester [e.g. ethynyl ester, propynyl ester, etc.];

ar(lower)alkyl ester which may have suitable substituent(s) [e.g. benzyl ester, 4-methoxybenzyl ester, 4-nitrobenzyl ester, phenethyl ester, trityl ester, benzhydryl ester, bis(methoxyphenyl)methyl ester, 3,4-dimethoxybenzyl ester, 4-hydroxy-3,5-di-tert-butylbenzyl ester, etc.];

aryl ester which may have suitable substituent(s) [e.g. phenyl ester, 4-chlorophenyl ester, tolyl ester, 4-tert-butylphenyl ester, xylyl ester, mesityl ester, cumenyl ester, etc.]; or the like.

Suitable examples of the "protected carboxy-(lower)alkynyloxy(lower)alkyl" thus defined may be (lower)alkoxycarbonyl(lower)alkynyloxy(lower)alkyl such as methoxycarbonylethynyloxymethyl, 3-ethoxycarbonyl-2-propynyloxymethyl, 1-ethoxycarbonyl-2-propynyloxymethyl, 2-(3-ethoxycarbonyl-2-propynyloxy)ethyl, 1-(1-propoxycarbonyl-2-butynyloxy)propyl, 1-(4-ethoxycarbonyl-3-butynyloxy)-propyl, 2-(4-butoxycarbonyl-3-butynyloxy)butyl, 3-(4-tert-butoxycarbonyl-3-butynyloxy)butyl, 4-(3-pentyloxycarbonyl-1-pentynyloxy)pentyl, 4-(5-ethoxycarbonyl-4-pentynyloxy)pentyl, 5-(1-hexyloxycarbonyl-5-hexynyloxy)hexyl, 6-(6-hexyloxycarbonyl-5-hexynyloxy)hexyl, and the like, in which the preferred one may be (C₁-C₄)alkoxycarbonyl-(C₂-C₄)alkynyloxy(C₁-C₄)alkyl and the more preferred one may be 3-ethoxycarbonyl-2-propynyloxymethyl.

Suitable "carboxy(lower)alkynyl" may be the same as that in the terms of "carboxy(lower)alkynyloxy(lower)alkyl" and may include carboxyethynyl, 3-carboxy-2-propynyl, 1-carboxy-2-propynyl, 1-carboxy-2-butylnyl, 4-carboxy-3-butylnyl, 3-carboxy-1-pentynyl, 1-carboxy-5-hexynyl, 6-carboxy-5-hexynyl, and the like, in which the preferred one may be carboxy(C₂-C₄)alkynyl and the more preferred one may be 3-carboxy-2-propynyl.

Suitable "protected carboxy(lower)alkynyl" may be the same as that in the terms of "protected carboxy(lower)alkynyloxy(lower)alkyl" and may include lower alkoxycarbonyl(lower)alkynyl such as methoxycarbonylethynyl, 3-ethoxycarbonyl-2-propynyl, 1-ethoxycarbonyl-2-propynyl, 1-propoxycarbonyl-2-butynyl, 4-ethoxycarbonyl-3-butynyl, 4-butoxycarbonyl-3-butynyl, 4-tert-butoxycarbonyl-3-butynyl, 3-pentyloxycarbonyl-1-pentynyl, 1-hexyloxycarbonyl-5-hexynyl, 6-hexyloxycarbonyl-5-hexynyl, and the like, in which the preferred one may be (C₁-C₄)alkoxycarbonyl(C₂-C₄)alkynyl and the more preferred one may be 3-ethoxycarbonyl-2-propynyl.

"(ω-Lower alkynyloxy)(lower)alkyl" means the above-defined lower alkynyloxy(lower)alkyl group, in which the triple bond always exists on the terminal carbon atom of the lower alkynyl moiety, and suitable examples of such "(ω-lower alkynyloxy)(lower)alkyl" may include ethynyloxymethyl, 2-propynyloxymethyl, 2-(2-propynyloxy)ethyl, 1-(3-butynyloxy)propyl, 2-(3-butynyloxy)butyl, 4-(4-pentynyloxy)pentyl, 6-(5-hexynyloxy)hexyl, and the like, in which the preferred one may be [ω-(C₂-C₄)alkynyloxy](C₁-C₄)alkyl and the more preferred one may be 2-propynyloxymethyl.

"(ω-Carboxy-ω-lower alkynyloxy)(lower)alkyl" means the above-defined ω-lower alkynyloxy(lower)alkyl group which is substituted with carboxy on the terminal carbon atom of the lower alkynyl moiety, and suitable examples of such "(ω-carboxy-ω-lower alkynyloxy)(lower)alkyl" may include carboxyethynyloxymethyl, 3-carboxy-2-propynyloxymethyl, 2-(3-carboxy-2-propynyloxy)ethyl, 1-(4-carboxy-3-butynyloxy)propyl, 2-(4-carboxy-3-butynyloxy)butyl, 4-(5-carboxy-4-pentynyloxy)pentyl,

6-(6-carboxy-5-hexynyloxy)hexyl and the like, in which the preferred one may be [ω -carboxy- ω -(C_2 - C_4)alkynyloxy]-(C_1 - C_4)alkyl and the more preferred one may be 3-carboxy-2-propynyloxymethyl.

5 "(ω -Protected carboxy- ω -lower alkynyloxy) (lower)-alkyl" means the above-defined ω -lower alkynyloxy(lower)-alkyl group which is substituted with protected carboxy as mentioned above on the terminal carbon atom of the lower alkynyl moiety, and suitable examples of such
10 "(ω -protected carboxy- ω -lower alkynyloxy) (lower)alkyl" may be (ω -lower alkoxycarbonyl- ω -lower alkynyloxy) (lower)alkyl such as methoxycarbonylethynyloxymethyl, 3-ethoxycarbonyl-2-propynyloxymethyl, 2-(3-ethoxycarbonyl-2-propynyloxy)ethyl, 1-(4-propoxycarbonyl-3-butynyloxy)propyl, 3-(4-tert-butoxycarbonyl-3-butynyloxy)butyl, 4-(5-pentyloxycarbonyl-4-pentynyloxy)pentyl, 5-(6-hexyloxycarbonyl-5-hexynyloxy)hexyl, and the like, in which the preferred one may be [ω -(C_1 - C_4)alkoxycarbonyl- ω -(C_2 - C_4)alkynyloxy]-(C_1 - C_4)alkyl and the more preferred one may be 3-ethoxycarbonyl-2-propynyloxymethyl.

Suitable "aryl" may include phenyl, tolyl, xylyl, 1-naphthyl, 2-naphthyl, 1-anthryl, 2-anthryl, and the like, in which the preferred one may be phenyl.

15 Suitable "ar(lower)alkyl" may include mono-(or di- or tri-)phenyl(lower)alkyl such as benzyl, 1-phenylethyl, 2-phenylethyl, 2-phenylpropyl, 3-phenylbutyl, 1-methyl-2-phenylpropyl, 5-phenylpentyl, 4-phenylhexyl, benzhydryl, 2,3-diphenylpropyl, trityl, 1,2,3-triphenylbutyl, etc.;

10 naphthyl(lower)alkyl such as 1-naphthylmethyl, 2-naphthylmethyl, 1-(2-naphthyl)ethyl, 3-(1-naphthyl)propyl, 2-(2-naphthyl)butyl, 5-(1-naphthyl)pentyl, 4-(2-naphthyl)hexyl, etc.;

15 and the like, in which the preferred one may be

phenyl(C₁-C₄)alkyl and naphthyl(C₁-C₄)alkyl, and the more preferred one may be benzyl, 1-phenylethyl, 2-phenylethyl, 1-naphthylmethyl and 2-naphthylmethyl.

Said "ar(lower)alkyl" may have one or more (preferably 1 to 3) suitable substituent(s) selected from a group consisting of lower alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, pentyl, hexyl, etc.) and halogen (e.g. fluoro, chloro, bromo, iodo), and the preferred examples of said substituted ar(lower)alkyl may be mono or di halophenyl(lower)alkyl (e.g. 2-chlorobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 2-bromobenzyl, 4-bromobenzyl, 2-fluorobenzyl, 4-fluorobenzyl, 4-iodobenzyl, 2-chlorophenethyl, 2,3-dichlorobenzyl, 2,4-dichlorobenzyl, 3,4-dichlorobenzyl, 2,6-dichlorobenzyl, 2-chloro-4-fluorobenzyl, etc.), mono or di(lower)alkylphenyl(lower)alkyl (e.g. 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl, 2-methylphenethyl, 2-ethylbenzyl, 2-propylbenzyl, 2-isopropylbenzyl, 3-butylbenzyl, 4-pentylbenzyl, 2-hexylbenzyl, 2,3-dimethylbenzyl, 2,6-dimethylbenzyl, 2,4-diethylbenzyl, 2-methyl-4-propylbenzyl, etc.), and the more preferred one may be mono or dihalophenyl(C₁-C₄)alkyl and mono or di(C₁-C₄)alkyl phenyl(C₁-C₄)alkyl, and the most preferred one may be 2-chlorobenzyl, 3-chlorobenzyl, 2-bromobenzyl, 2-fluorobenzyl, 2,4-dichlorobenzyl, 3,4-dichlorobenzyl, 2,6-dichlorobenzyl, 2-methylbenzyl, 2-ethylbenzyl, 2-isopropylbenzyl and 2,6-dimethylbenzyl.

Suitable "ar(lower)alkenyl" may include mono(or di or tri)-phenyl(lower)alkenyl such as styryl, cinnamyl, phenylbutenyl (e.g. 4-phenyl-2-butenyl, 2-phenyl-3-butenyl, etc.), phenylpentenyl (e.g. 1-phenyl-1-pentenyl, etc.), phenylhexenyl (e.g. 4-phenyl-2-hexenyl, etc.), 2,3-diphenyl-1-butenyl, 2,3,4-triphenyl-4-pentenyl, and the like, in which

the preferred one may be phenyl(C₂-C₄)alkenyl and the more preferred one may be cinnamyl.

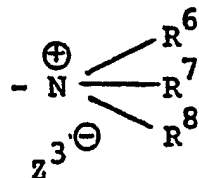
Suitable "condensed bicyclic hydrocarbon group" may include naphthyl, 1,4-dihydronaphthyl, indenyl, benzene-condensed cyclo(lower)alkyl (e.g. 1,2,3,4-tetrahydronaphthyl, 2,3-dihydroindenyl, etc.), perhydroindenyl and the like, in which the preferred one may be benzene-condensed cyclo(C₅-C₆)alkyl and the more preferred one may be 1,2,3,4-tetrahydronaphthyl.

Suitable "lower alkyl having cyclo(lower)alkyl" may include cyclopropylmethyl, cyclobutylmethyl, cyclopentylethyl, cyclohexylmethyl, cyclohexylethyl, cyclohexylpropyl, cyclohexylbutyl, cyclohexylpentyl, cyclohexylhexyl, and the like, in which the preferred one may be cyclo(C₅-C₆)alkyl(C₁-C₄)alkyl and the more preferred one may be cyclohexylmethyl.

Suitable "lower alkylene" may include methylene, ethylene, trimethylene, propylene, tetramethylene, pentamethylene, hexamethylene and the like, in which the preferred one may be C₁-C₄alkylene and the more preferred one may be methylene.

Suitable "an acid residue" may include halogen (e.g. fluorine, chlorine, bromine, iodine), acyloxy (e.g. acetoxy, tosyloxy, mesyloxy, etc.), and the like.

Suitable "a leaving group" may include an acid residue as mentioned above, a group of the formula:



wherein R⁶, R⁷ and R⁸ are each lower alkyl as mentioned above, and

Z^3 is an acid residue as mentioned above, and the like.

The processes for preparing the object compounds of the present invention are explained in detail in the following.

Process 1

The object compound (I) or a salt thereof can be prepared by reacting the compound (II) or a salt thereof with the compound (III) or a salt thereof.

Suitable salts of the compound (II) can be referred to the acid addition salt as exemplified for the compound (I) and those of the compound (III) can be referred to the salt with a base for the same.

This reaction is usually carried out in a solvent such as alcohol [e.g. methanol, ethanol, etc.], benzene, N,N-dimethylformamide, tetrahydrofuran, diethyl ether or any other solvent which does not adversely affect the reaction.

The reaction may be carried out in the presence of an inorganic or an organic base such as an alkali metal hydroxide [e.g. sodium hydroxide, potassium hydroxide, etc.], an alkali metal carbonate [e.g. sodium carbonate, potassium carbonate, etc.], an alkali metal bicarbonate [e.g. sodium bicarbonate, potassium bicarbonate, etc.], tri(lower)alkylamine [e.g. trimethylamine, triethylamine, etc.], pyridine or its derivative [e.g. picoline, lutidine, 4-dimethylaminopyridine, etc.], or the like. In case that the base to be used is liquid, it can also be used as a solvent.

The reaction temperature is not critical, and the reaction can be carried out under cooling, at

ambient temperature or under warming or heating.

Process 2

5 The object compound (I_b) or a salt thereof can
be prepared by subjecting the compound (I_a) or a salt
thereof to isomerization reaction of lower alkynyl
into cumulated lower alkadienyl.

10 Suitable salts of the compounds (I_a) and (I_b)
can be referred to the acid addition salts as exemplified
for the compound (I).

15 This reaction is usually carried out in the
presence of a base such as an alkali metal hydroxide
(e.g. sodium hydroxide, potassium hydroxide, etc.),
an alkali metal carbonate (e.g. sodium carbonate,
potassium carbonate, etc.), or the like.

20 This reaction is usually carried out in a solvent
such as alcohol (e.g. methanol, ethanol, etc.),
N,N-dimethylformamide or any other solvent which does
not adversely affect the reaction.

25 The reaction temperature is not critical, and
the reaction can be carried out at ambient temperature
or under warming or heating.

Process 3

30 The object compound (I_c) or a salt thereof can
be prepared by reacting the compound (IV) or a salt
thereof with the compound (V) or a salt thereof.

35 Suitable salts of the compound (IV) can be
referred to the acid addition salts as exemplified
for the object compound (I).

40 Suitable salts of the compound (I_c) can be
referred to the ones as exemplified for the object
compound (I).

45 Suitable salts of the compound (V) are salts with

a base such as an alkali metal salt (e.g. sodium salt, potassium salt, lithium salt, etc.), or the like.

This reaction is usually carried out in the presence of a base such as alkali metal hydride (e.g. sodium hydride, potassium hydride, lithium hydride, etc.), alkali metal alkoxide (e.g. potassium t-butoxide, etc.), an alkali metal (e.g. sodium, potassium, lithium, etc.) or the like.

This reaction is usually carried out in a solvent such as alcohol [e.g. methanol, ethanol, etc.], dimethyl sulfoxide, benzene, N,N-dimethylformamide, tetrahydrofuran, diethyl ether or any other solvent which does not adversely affect the reaction.

In case that the compound (V) or a salt thereof to be used is liquid, it can also be used as a solvent.

The reaction temperature is not critical, and the reaction can be carried out under cooling, at ambient temperature or under warming or heating.

Process 4

The object compound (Ie) or a salt thereof can be prepared by subjecting the compound (Id) or a salt thereof to acylation reaction.

Suitable salts of the compound (Id) can be referred to the acid addition salts as exemplified for the compound (I).

Suitable salts of the compound (Ie) can be referred to the ones as exemplified for the compound (I).

The acylation reaction of this process can be carried out by reacting the compound (Id) or a salt thereof with a conventional agent which can introduce a carboxy or a protected carboxy group into a terminal carbon atom of ω -lower alkynyl such as carbon dioxide gas, dry ice, lower alkoxy(halo)formate (e.g.

ethyl chloroformate, etc.), di(lower)alkyl carbonate

(e.g. dimethyl carbonate, diethyl carbonate, etc.), di(lower)alkyl oxalate (e.g. diethyl oxalate, etc.), tri(lower)alkyl phosphonoacetate (e.g. triethyl phosphonoacetate, etc.).

5 This reaction is usually carried out in the presence of a base such as metalated lower alkyl (e.g. methyl lithium, n-butyl lithium, etc.), metalated aryl (e.g. phenyl lithium, etc.), alkali metal hydride (e.g. sodium hydride, potassium hydride, etc.) or the like.

10 This reaction is usually carried out in a solvent such as diethyl ether, tetrahydrofuran, N,N-dimethylformamide, n-hexane or any other solvent which does not adversely affect the reaction.

15 The reaction temperature is not critical, and the reaction can be carried out under cooling or at ambient temperature.

20 The object compounds (I) and their pharmaceutically acceptable salts of the present invention are novel and exhibit high antiulcerative activity.

 In order to illustrate the usefulness of the object compounds (I), the pharmacological data of some representative compounds of the object compounds (I) are shown in the following.

25 (A) Inhibition on ethanol ulcer

Test Method :

30 Five male Sprague-Dawley rats, aged 7-weeks and weighing about 200 g, were used per group for the study on ethanol ulcer after the fast for 24 hours.

 Test compound was suspended in 0.1% methylcellulose aqueous solution, and the suspension (5 ml/kg) was orally given to each rat.

35 The control group was given a vehicle, i.e. 0.1% methylcellulose aqueous solution (5 ml/kg), alone in

the same way.

Absolute ethanol (5 ml/kg) was orally administered 30 minutes after dosing with test compound, and one hour later, the rats were sacrificed and their stomachs were removed. The area of ulcers of each rat was measured. The mean area (mm) in the medicated group was compared with that in the control group.

Test compounds

- (1) 8-(2-Methylbenzyloxy)-3-(2-propynyloxymethyl)-2-methylimidazo[1,2-a]pyridine
- (2) 8-(2-Chlorobenzyloxy)-3-(2-propynyloxymethyl)-2-methylimidazo[1,2-a]pyridine
- (3) 8-(2-Methylbenzyloxy)-3-(2-propynyl)-2-methylimidazo[1,2-a]pyridine

Test Results

A) Inhibition % at the dose of 32 mg/kg :

Test Compound	Inhibition %
(1)	94.4
(2)	98.2
(3)	91.8

B) The ED₅₀ value of the Test Compound (1) : 1.1 mg/kg

(B) Inhibition on stress ulcer

Test Method :

Five Sprague-Dawley rats weighing about 200 g were used per group. Each animal was immobilized in a small cage and put in a water bath allowing to respire. The temperature of the water bath kept at

22°C. The test compound was administered orally just before the immobilization. Seven hours later, the animals were sacrificed and their stomachs were removed. The stomach was then fixed with 2% formalin. The area of ulcers was measured for each animal. The mean area (mm²) in the medicated animals was compared with that in the control animals.

Test Compounds

- (1) 8-(2-Methylbenzyloxy)-3-(2-propynyloxymethyl)-2-methylimidazo[1,2-a]pyridine
- (2) 8-(2-Chlorobenzyloxy)-3-(2-propynyloxymethyl)-2-methylimidazo[1,2-a]pyridine
- (3) 8-(2-Methylbenzyloxy)-3-(2-propynyl)-2-methylimidazo[1,2-a]pyridine

Test Results

A) Inhibition % at the dose of 32 mg/kg :

Test Compound	Inhibition %
(1)	100
(2)	100
(3)	100

B) The ED₅₀ value of the Test Compound (1) : 0.15 mg/kg

As being apparent from the above test results, the object compound (I) of the present invention are useful as an antiulcerative agent.

For therapeutic purpose, the compounds according to the present invention can be used in a form of

pharmaceutical preparation containing said compound
as an active ingredient, in admixture with a pharma-
ceutically acceptable carrier such as an organic or
inorganic solid or liquid excipient suitable for oral
5 or parenteral administration. The pharmaceutical
preparations may be capsules, tablets, dragees,
solution, suspension, emulsion, and the like. If
desired, there may be included in the above preparations
auxiliary substances, stabilizing agents, wetting or
10 emulsifying agents, buffers and other commonly used
additives.

While the dosage of the compounds will vary
depending upon the age and condition of the patient,
an average single dose of about 5 mg, 10 mg, 50 mg,
15 100 mg, 250 mg, 500 mg, and 1000 mg. of the compounds
according to the present invention may be effective
for treating ulcer. In general, amounts between
1 mg/body and about 2,000 mg/body or even more may
be administered per day.

The following preparations and examples are given for the purpose of illustrating the present invention.

Preparation 1

A solution of 5-hexen-2-one (3.92 g) in N,N-dimethylformamide (4 ml) was added to mixture of cupric chloride dihydrate (13.636 g) and lithium chloride (3.392 g) in N,N-dimethylformamide (20 ml) at 80°C. After being stirred at 80-90°C for 1 hour, the mixture was poured into cold water and extracted with ethyl acetate. The extract was washed with water, dried over magnesium sulfate and evaporated in vacuo to give a crude oil of 3-chloro-5-hexen-2-one (3.01 g) which was used for the next step without purification.

Preparation 2

Tosyl chloride (3.81 g) was added to a solution of 3-hydroxy-5-hexyn-2-one (2.24 g) and triethylamine (2.424 g) in methylene chloride (20 ml) under ice-cooling. After being stirred for 2.5 hours, the mixture was washed with water, dried over magnesium sulfate and evaporated in vacuo. The oily residue was purified by column chromatography on silica gel (60 g) using methylene chloride as an eluent to give an oil of 3-tosyloxy-5-hexyn-2-one (2.94 g).

IR (film/NaCl) : 3280, 1720, 1590, 1360 (broad) cm^{-1}

NMR (CCl_4 , δ) : 1.79 (1H, t, $J=2\text{Hz}$), 2.25 (3H, s), 2.43 (3H, s), 2.3-2.6 (2H, m), 4.66 (1H, t, $J=5\text{Hz}$), 7.31 (2H, d, $J=8\text{Hz}$), 7.78 (2H, d, $J=8\text{Hz}$).

Preparation 3

Mesyl chloride (1.73 ml) was added dropwise to a solution of 3-hydroxy-2-methoxy-1-hexen-5-yne (2 g) and triethylamine (3.32 ml) in methylene chloride (20 ml)

under ice-cooling over a period of 10 minutes. After being stirred for 48 hours at room temperature the mixture was washed successively with water, aqueous sodium bicarbonate solution, and brine, dried over magnesium sulfate, and evaporated in vacuo to give 3-mesyloxy-2-methoxy-1-hexen-5-yne (3.45 g).

IR (film/NaCl) : 3280, 2110 cm^{-1}

NMR (CCl_4 , δ) : 1.96 (1H, t, $J=3\text{Hz}$), 2.63-2.80 (2H, m), 2.95 (3H, s), 3.62 (3H, s), 4.22 (1H, d, $J=3\text{Hz}$), 4.40 (1H, d, $J=3\text{Hz}$), 4.93 (1H, t, $J=6\text{Hz}$)

Preparation 4

To a solution of 3-mesyloxy-2-methoxy-1-hexen-5-yne (0.5 g) in acetone (1.5 ml) was added 20% sulfuric acid (1.5 ml) under ice-cooling and the mixture was stirred for 1.5 hours under the same conditions and then for 1.5 hours at room temperature. Acetone was evaporated in vacuo and the residue was extracted with methylene chloride. The extract was washed successively with water, aqueous sodium bicarbonate solution, and brine, dried over magnesium sulfate, and evaporated in vacuo to give 3-mesyloxy-5-hexyn-2-one (0.41 g).

IR (film/NaCl) : 3290, 2120, 1720 cm^{-1}

NMR (CCl_4 , δ) : 2.03 (1H, t, $J=3\text{Hz}$), 2.31 (3H, s) 2.70-2.86 (2H, m), 3.11 (3H, s), 4.92 (1H, t, $J=6\text{Hz}$)

Preparation 5

To a mixture of 2-amino-3-hydroxypyridine (7 g) and Adogen 464 (Trademark : prepared by Aldrich Chemical Co.) (0.4 g) in 40% aqueous sodium hydroxide (32 ml) and methylene chloride (32 ml) was added 2-methylbenzyl chloride (8.42 ml) at ambient temperature. After being stirred for 24 hours, the organic layer was separated

and the aqueous layer was extracted with methylene chloride. The combined extracts were washed with saturated sodium chloride aqueous solution, dried over magnesium sulfate, and evaporated in vacuo. The crystalline residue was recrystallized from ethyl acetate to give 2-amino-3-(2-methylbenzyloxy)pyridine (7.56 g).

mp : 100 to 101°C

IR (Nujol) : 3450, 3275, 3125, 1625 cm^{-1}

NMR (CDCl_3 , δ) : 2.40 (3H, s), 4.68 (2H, s),
5.05 (2H, s), 6.43-6.73 (1H, m),
6.98 (1H, dd, $J=2\text{Hz}$ and 8Hz), 7.10-7.46
(4H, m), 7.66 (1H, dd, $J=2\text{Hz}$ and 5Hz)

Preparation 6

The following compounds were prepared according to a similar manner to that of Preparation 5.

(1) 2-Amino-3-(2-ethylbenzyloxy)pyridine

mp : 93 to 95°C (recrystallized from a mixture of ethyl acetate and n-hexane)

IR (Nujol) : 3475, 3275, 3130, 1620 cm^{-1}

NMR (CDCl_3 , δ) : 1.27 (3H, t, $J=8\text{Hz}$),
2.73 (2H, q, $J=8\text{Hz}$), 4.68 (2H, broad s),
5.07 (2H, s), 6.43-6.73 (1H, m), 6.99 (1H,
d, $J=7\text{Hz}$), 7.12-7.50 (4H, m), 7.66 (1H, dd,
 $J=2\text{Hz}$ and 5Hz)

(2) 2-Amino-3-(2-isopropylbenzyloxy)pyridine

mp : 106 to 107°C (recrystallized from a mixture of ethyl acetate and n-hexane)

IR (Nujol) : 3450, 3275, 3120, 1620 cm^{-1}

NMR (CDCl_3 , δ) : 1.25 (6H, d, $J=6\text{Hz}$),
2.50-3.45 (1H, m), 4.63 (2H, broad s),
5.05 (2H, s), 6.43-6.75 (1H, m),
7.02 (1H, d, $J=8\text{Hz}$), 7.15-7.48 (4H, m),
7.66 (1H, dd, $J=2\text{Hz}$ and 5Hz)

(3) 2-Amino-3-(2-chlorobenzyloxy)pyridine

mp : 100 to 101°C (recrystallized from methylene chloride)

IR (Nujol) : 3465, 3275, 3120, 1620 cm^{-1}

5

NMR (CDCl_3 , δ) : 4.73 (2H, broad s),
5.15 (2H, s), 6.40-6.70 (1H, m),
6.92 (1H, dd, $J=2\text{Hz}$ and 8Hz), 7.10-7.50
(4H, m), 7.65 (1H, dd, $J=2\text{Hz}$ and 5Hz)

10

(4) 2-Amino-3-(3-chlorobenzyloxy)pyridine

mp : 87.5 to 89°C (recrystallized from a mixture of methylene chloride and n-hexane)

IR (Nujol) : 3480, 3275, 3100, 1622 cm^{-1}

15

NMR (CDCl_3 , δ) : 4.88 (2H, broad s), 4.97 (2H, s),
6.40-6.63 (1H, m), 6.89 (1H, d, $J=8\text{Hz}$),
7.27 (3H, s), 7.38 (1H, s), 7.65 (1H, dd,
 $J=2\text{Hz}$ and 5Hz)

20

(5) 2-Amino-3-(2-bromobenzyloxy)pyridine

mp : 107 to 108°C (recrystallized from ethyl acetate)

IR (Nujol) : 3440, 3270, 3125, 1617 cm^{-1}

25

NMR (CDCl_3 , δ) : 4.80 (2H, broad s), 5.11 (2H, s),
6.46-6.70 (1H, m), 6.94 (1H, dd, $J=1.5\text{Hz}$ and
 7.5Hz), 7.06-7.76 (5H, m)

30

(6) 2-Amino-3-(2,6-dimethylbenzyloxy)pyridine

mp : 151 to 155°C (recrystallized from a mixture of ethyl acetate and n-hexane)

IR (Nujol) : 3470, 3280, 3145, 1620 cm^{-1}

NMR (CDCl_3 , δ) : 2.47 (6H, s), 4.68 (2H, broad s),
5.01 (2H, s), 6.48-6.71 (1H, m),
6.97-7.28 (4H, m), 7.68 (1H, dd, $J=2\text{Hz}$ and
 5Hz)

35

(7) 2-Amino-3-(2,6-dichlorobenzyloxy)pyridine

mp : 146 to 148°C (recrystallized from methanol)

IR (Nujol) : 3455, 3270, 3125, 1620 cm^{-1}

NMR (CDCl_3 , δ) : 4.70 (2H, broad s),

5.28 (2H, s), 6.45-6.73 (1H, m),

7.02-7.53 (4H, m), 7.67 (1H, dd, $J=2\text{Hz}$ and 5Hz)

(8) 2-Amino-3-(2-naphthylmethoxy)pyridine

mp : 138 to 139°C

NMR (CDCl_3 , δ) : 4.73 (2H, broad s), 5.22 (2H, s),

6.40-6.70 (1H, m), 6.96 (1H, dd, $J=2\text{Hz}$ and

7Hz), 7.30-8.0 (8H, m)

(9) 2-Amino-3-(1-naphthylmethoxy)pyridine

mp : 146 to 148°C (recrystallized from ethyl acetate)

NMR (CDCl_3 , δ) : 4.72 (2H, broad s), 5.38 (2H, s),

6.36 (1H, dd, $J=5\text{Hz}$ and 8Hz), 7.02 (1H, d,

$J=8\text{Hz}$), 7.30-8.13 (8H, m)

(10) 2-Amino-3-cinnamyloxypyridine (trans isomer)

mp : 127 to 129°C (recrystallized from a mixture of ethyl acetate and n-hexane)

IR (Nujol) : 3475, 3275, 3120, 1620 cm^{-1}

NMR (CDCl_3 , δ) : 4.66 (2H, d, $J=5\text{Hz}$),

4.79 (2H, broad s), 6.14-7.02 (4H, m),

7.20-7.48 (5H, m), 7.66 (1H, dd, $J=2\text{Hz}$ and 5Hz)

(11) 2-Amino-3-(1,2,3,4-tetrahydro-1-naphthyloxy)pyridine

mp : 106.5 to 107°C (recrystallized from a mixture of ethyl acetate and n-hexane)

IR (Nujol) : 3475, 3300, 3140, 1626 cm^{-1}

NMR (CDCl_3 , δ) : 1.60-2.36 (4H, m),

2.63-3.06 (2H, m), 4.63 (2H, broad s),
5.20-5.46 (2H, m), 6.46-6.75 (1H, m),
6.98-7.50 (5H, m), 7.65 (1H, dd, J=1Hz
and 5Hz)

5

(12) 2-Amino-3-cyclohexylmethoxypyridine

mp : 110 to 112°C

NMR (CDCl₃, δ) : 0.63-2.10 (11H, m), 3.78 (2H,
d, J=6Hz), 4.69 (2H, broad s), 6.43-6.73
(1H, m), 6.90 (1H, dd, J=2Hz and 8Hz),
7.64 (1H, dd, J=2Hz and 5Hz)

10

Preparation 7

Molecular Sieves (16 g) was added to a solution of
2,3-diaminopyridine (8 g), 2-methylbenzaldehyde (8.81 g),
and acetic acid (4.2 ml) in methanol (160 ml) and the
mixture was stirred for 96 hours at room temperature.
Sodium cyanoborohydride (4.61 g) was added portionwise
to the mixture with stirring under ice-cooling over a
period of 20 minutes. After being stirred for 3 hours,
the mixture was made alkaline with aqueous sodium
bicarbonate solution and filtered by suction. The
filtrate was evaporated in vacuo, and to the residue
was added water and then extracted with methylene
chloride. The extract was washed with brine, dried over
magnesium sulfate, and evaporated in vacuo. The
crystalline residue was recrystallized from a mixture of
ethyl acetate and n-hexane to give 2-amino-3-(2-
methylbenzylamino)pyridine (5.38 g).

20

25

30

mp : 135 to 140°C

NMR (CDCl₃, δ) : 2.36 (3H, s), 3.20-3.63 (1H,
broad s), 4.20 (2H, broad d, J=4Hz),
4.40-5.20 (2H, broad s), 6.50-6.93 (2H, m),
7.0-7.63 (5H, m)

35

Preparation 8

2-Amino-3-(2-chlorobenzylamino)pyridine was obtained according to a similar manner to that of Preparation 7.

mp : 144 to 147°C

5 NMR (CDCl₃, δ) : 3.60-4.60 (3H, m), 4.36 (2H, d, J=6Hz), 6.43-6.83 (2H, m), 6.96-7.86 (5H, m)

Preparation 9

10 To a solution of 2-methylbenzyl alcohol (0.985 g) in N,N-dimethylformamide (10 ml) was added 62.8% sodium hydride (0.308 g) under a nitrogen atmosphere and then stirred for 30 minutes. 2-Amino-3-chloropyrazine (0.87 g) was added to the solution and the mixture was heated at 65°C for 2 hours and poured onto crushed ice.
15 The resulting precipitates were collected by filtration, washed with n-hexane, and dried in a desiccator to give 2-amino-3-(2-methylbenzyloxy)pyrazine (0.6 g).

mp : 70 to 72°C

20 NMR (CDCl₃, δ) : 2.37 (3H, s), 4.40-5.00 (2H, broad s), 5.34 (2H, s), 7.00-7.45 (4H, m), 7.35 (1H, d, J=3Hz), 7.48 (1H, d, J=3Hz)

Preparation 10

25 A mixture of 2-amino-3-chloropyrazine (4.3 g), 2-methylbenzylamine (4.6 g), potassium carbonate (5.5 g), and potassium iodide (0.4 g) in N,N-dimethylformamide (43 ml) was refluxed for 24 hours under a nitrogen atmosphere and allowed to stand at room temperature. The mixture was poured into water and extracted with
30 ethyl acetate. The extract was washed with water, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (110 g) with a mixture of chloroform and methanol (100:3) as an eluent to give 2-amino-3-(2-
35 methylbenzylamino)pyrazine (1.4 g).

NMR (CDCl_3 , δ) : 2.33 (3H, s), 3.80-4.50 (3H, broad s), 4.50 (2H, d, $J=5\text{Hz}$), 6.95-7.35 (4H, m), 7.30 (1H, d, $J=3\text{Hz}$), 7.50 (1H, d, $J=3\text{Hz}$)

5

Preparation 11

A 60% dispersion of sodium hydride in mineral oil (1.87 g) was added portionwise to a suspension of 8-hydroxy-2-methylimidazo[1,2-a]pyridine (6.3 g) in dimethyl sulfoxide (63 ml) at room temperature over a period of 15 minutes. After being stirred for 30 minutes, 2-chlorobenzyl chloride (7.54 g) was added in one portion to the mixture and then the resultant mixture was stirred for 24 hours at room temperature. The mixture was poured into water and the resulting precipitate was collected by filtration. The crude product was purified by column chromatography on silica gel (30 g) with methylene chloride as an eluent to afford a solid, which was recrystallized from a mixture of diethyl ether and n-hexane to give 8-(2-chlorobenzyloxy)-2-methylimidazo[1,2-a]pyridine (7.75 g).

mp : 97 to 98°C

IR (Nujol) : 1535, 1280, 1260, 1100 cm^{-1}

NMR (CDCl_3 , δ) : 2.46 (3H, s), 5.41 (2H, s), 6.26-6.73 (2H, m), 7.05-7.50 (4H, m), 7.52-7.83 (2H, m)

Preparation 12

The following compounds were obtained according to a similar manner to that of Preparation 11.

(1) 8-(2-Methylbenzyloxy)-2-methylimidazo[1,2-a]pyridine

mp : 101 to 103°C (recrystallized from a mixture of ethyl acetate and n-hexane)

IR (Nujol) : 1530, 1485, 1275, 1260, 1095 cm^{-1}

NMR (CDCl_3 , δ) : 2.36 (3H, s), 2.43 (3H, s),
5.23 (2H, s), 6.28-6.63 (2H, m), 7.0-7.53
(5H, m), 7.59 (1H, dd, $J=1.5\text{Hz}$ and 6Hz)

(2) 8-(1-Phenylethoxy)-2-methylimidazo[1,2-a]pyridine

NMR (CDCl_3 , δ) : 1.80 (3H, d, $J=7\text{Hz}$), 2.52 (3H, s),
5.50 (1H, q, $J=7\text{Hz}$), 6.06-6.56 (2H, m),
6.93-7.66 (7H, m)

(3) 8-(3-Chlorobenzyloxy)-2-methylimidazo[1,2-a]-
pyridine

mp : 108 to 110°C (recrystallized from a mixture
of ethyl acetate and n-hexane)

IR (Nujol) : 1590, 1530, 1490, 1275, 1260, 1160,
1100 cm^{-1}

NMR (CDCl_3 , δ) : 2.46 (3H, s), 5.26 (2H, s),
6.25-6.75 (2H, m), 7.15-7.45 (4H, m),
7.50 (1H, s), 7.63 (1H, dd, $J=2\text{Hz}$ and 6Hz)

(4) 8-(2-Bromobenzyloxy)-2-methylimidazo[1,2-a]pyridine

mp : 113 to 114°C (recrystallized from diethyl
ether)

NMR (CDCl_3 , δ) : 2.54 (3H, s), 5.43 (2H, s),
6.29-6.76 (2H, m), 7.10-7.80 (6H, m)

(5) 8-(2,6-Dichlorobenzyloxy)-2-methylimidazo[1,2-a]-
pyridine

mp : 157 to 160°C

NMR (CDCl_3 , δ) : 2.43 (3H, s), 5.45 (2H, s),
6.46-6.76 (2H, m), 7.13-7.46 (4H, m),
7.56-7.76 (1H, m)

(6) 8-(2,4-Dichlorobenzyloxy)-2-methylimidazo[1,2-a]-
pyridine

mp : 140 to 141°C (recrystallized from ethyl acetate)

IR (Nujol) : 1280, 1100 cm^{-1}

NMR (CDCl_3 , δ) : 2.50 (3H, s), 5.36 (2H, s),
6.20-6.73 (2H, m), 7.10-7.80 (5H, m)

5 Preparation 13

A solution of 2-amino-3-(2-methylbenzylamino)-
pyridine (3.25 g) and chloroacetone (1.26 ml) in ethanol
(65 ml) was refluxed for 18 hours and then evaporated
in vacuo. To the residue was added aqueous sodium
bicarbonate solution and the mixture was extracted with
methylene chloride. The extract was washed with brine,
dried over magnesium sulfate, and evaporated in vacuo.
The oily residue was purified by column chromatography
on silica gel (40 g) with a mixture of methylene
chloride and ethyl acetate (10:1) as an eluent to give
8-(2-methylbenzylamino)-2-methylimidazo[1,2-a]pyridine
(1.80 g).

NMR (CDCl_3 , δ) : 2.38 (3H, s), 2.42 (3H, s),
4.40 (2H, d, $J=6\text{Hz}$), 5.06-5.46 (1H, broad s),
6.04 (1H, d, $J=7.5\text{Hz}$), 6.56 (1H, t, $J=7\text{Hz}$),
7.10-7.56 (6H, m)

Preparation 14

8-(2-Chlorobenzylamino)-2-methylimidazo[1,2-a]-
pyridine was obtained according to a similar manner to
that of Preparation 13.

NMR (CDCl_3 , δ) : 2.43 (3H, s), 4.56 (2H, d, $J=6\text{Hz}$),
5.36-5.76 (1H, m), 5.96 (1H, d, $J=7\text{Hz}$),
6.52 (1H, t, $J=7\text{Hz}$), 7.06-7.63 (6H, m)

Preparation 15

To a solution of 37% aqueous formaldehyde (2.38 g)
in acetic acid (38 ml) was added dropwise 50% aqueous
dimethylamine (2.63 g) with ice-cooling over a period
of 10 minutes and the mixture was stirred for an additional

10 minutes. The mixture was heated at 50-55°C for 2 hours after an addition of 8-(2-chlorobenzyloxy)-2-methylimidazo[1,2-a]pyridine (7.6 g) thereto and then evaporated in vacuo. The residue was basified with aqueous sodium hydroxide and extracted with methylene chloride. The extract was washed with water, dried over magnesium sulfate and evaporated in vacuo. The residual solid was recrystallized from a mixture of diethyl ether and n-hexane to give 8-(2-chlorobenzyloxy)-3-dimethylaminomethyl-2-methylimidazo[1,2-a]pyridine (7.85 g).

mp : 100 to 101°C

IR (Nujol) : 1550, 1295, 1285 cm^{-1}

NMR (CDCl_3 , δ) : 2.26 (6H, s), 2.50 (3H, s),
3.63 (2H, s), 5.43 (2H, s), 6.30-6.80 (2H, m),
7.10-7.46 (3H, m), 7.50-7.93 (2H, m)

Preparation 16

The following compounds were obtained according to a similar manner to that of Preparation 15.

(1) 8-(2-Methylbenzyloxy)-3-dimethylaminomethyl-2-methylimidazo[1,2-a]pyridine

mp : 65 to 67°C (recrystallized from petroleum ether)

IR (Nujol) : 1535, 1270, 1085, 1010 cm^{-1}

NMR (CDCl_3 , δ) : 2.21 (6H, s), 2.40 (3H, s),
2.45 (3H, s), 3.60 (2H, s), 5.26 (2H, s),
6.30-6.77 (2H, m), 7.07-7.56 (4H, m),
7.81 (1H, dd, $J=1.5\text{Hz}$ and 6Hz)

(2) 8-(1-Phenylethoxy)-3-dimethylaminomethyl-2-methylimidazo[1,2-a]pyridine

NMR (CDCl_3 , δ) : 1.80 (3H, d, $J=7\text{Hz}$), 2.23 (6H, s),
2.50 (3H, s), 3.60 (2H, s), 5.50 (1H, q, $J=7\text{Hz}$),

6.25 (1H, dd, J=1Hz and 6Hz), 6.46 (1H, t, J=6Hz), 7.16-7.56 (5H, m), 7.71 (1H, dd, J=1Hz and 6Hz)

- (3) 8-(3-Chlorobenzyloxy)-3-dimethylaminomethyl-2-methylimidazo[1,2-a]pyridine

mp : 71 to 72°C (recrystallized from a mixture of
of diethyl ether and n-hexane)

IR (Nujol) : 1540, 1290, 1275 cm^{-1}

NMR (CDCl_3 , δ) : 2.22 (6H, s), 2.46 (3H, s),
3.63 (2H, s), 5.29 (2H, s), 6.30-6.79 (2H, m),
7.16-7.46 (3H, m), 7.52 (1H, s),
7.83 (1H, dd, J=2Hz and 6Hz)

- (4) 8-(4-Chlorobenzyloxy)-3-dimethylaminomethyl-2-methylimidazo[1,2-a]pyridine

mp : 132 to 134°C

NMR ($\text{DMSO}-d_6$, δ) : 2.12 (6H, s), 2.30 (3H, s),
3.6 (2H, s), 5.25 (2H, s), 6.60-6.80 (2H, m),
7.45 (4H, s), 7.76-7.96 (1H, m)

- (5) 8-(2-Bromobenzyloxy)-3-dimethylaminomethyl-2-methylimidazo[1,2-a]pyridine

mp : 107 to 108°C (recrystallized from petroleum
ether)

NMR (CDCl_3 , δ) : 2.22 (6H, s), 2.46 (3H, s),
3.60 (2H, s), 5.37 (2H, s), 6.27-6.73 (2H, m),
6.93-7.73 (4H, m), 7.80 (1H, dd, J=2Hz and 6Hz)

- (6) 8-(2,6-Dichlorobenzyloxy)-3-dimethylaminomethyl-2-methylimidazo[1,2-a]pyridine

mp : 141 to 145°C

NMR (CDCl_3 , δ) : 2.25 (6H, s), 2.45 (3H, s),
3.63 (2H, s), 5.50 (2H, s), 6.53-6.83 (2H, m),

7.16-7.50 (3H, m), 7.85 (1H, dd, J=3Hz and 5Hz)

- 5 (7) 8-(3,4-Dichlorobenzyloxy)-3-dimethylaminomethyl-2-methylimidazo[1,2-a]pyridine

mp : 96 to 98°C

10 NMR (CDCl₃, δ) : 2.23 (6H, s), 2.46 (3H, s),
3.60 (2H, s), 5.25 (2H, s), 6.36-6.80 (2H, m),
7.20-7.66 (3H, m), 7.83 (1H, dd, J=2Hz and 7Hz)

- (8) 8-(2,4-Dichlorobenzyloxy)-3-dimethylaminomethyl-2-methylimidazo[1,2-a]pyridine

mp : 90 to 92°C

15 NMR (CDCl₃, δ) : 2.23 (6H, s), 2.46 (3H, s),
3.63 (2H, s), 5.36 (2H, s), 6.26-6.76 (2H, m),
7.23 (1H, dd, J=2Hz and 8Hz), 7.40 (1H, d, J=2Hz), 7.56 (1H, d, J=8Hz), 7.80 (1H, dd, J=2Hz and 7Hz)

- 20 (9) 8-Benzyloxy-3-dimethylaminomethylimidazo[1,2-a]-pyridine

mp : 86 to 87°C

25 NMR (CDCl₃, δ) : 2.23 (6H, s), 3.66 (2H, s),
5.33 (2H, s), 6.36-6.76 (2H, m), 7.20-7.60 (6H, m), 7.90 (1H, dd, J=2Hz and 6Hz)

- (10) 8-Benzyloxy-3-dimethylaminomethyl-2-phenylimidazo[1,2-a]pyridine

30 mp : 87 to 89°C (recrystallized from a mixture of ethyl acetate and n-hexane)

NMR (CDCl₃, δ) : 2.23 (6H, s), 3.83 (2H, s),
5.40 (2H, s), 6.30-6.80 (2H, m), 7.20-8.13 (11H, m)

(11) 8-(2-Methylbenzylamino)-3-dimethylaminomethyl-2-methylimidazo[1,2-a]pyridine

NMR (CDCl_3 , δ) : 2.22 (6H, s), 2.38 (6H, s),
 3.58 (2H, s), 4.36 (2H, d, $J=6\text{Hz}$),
 5.0-5.43 (1H, broad s), 6.06 (1H, d, $J=7\text{Hz}$),
 6.59 (1H, t, $J=7\text{Hz}$), 7.05-7.45 (4H, m),
 7.55 (1H, d, $J=7\text{Hz}$)

(12) 8-(2-Chlorobenzylamino)-3-dimethylaminomethyl-2-methylimidazo[1,2-a]pyridine

NMR (CDCl_3 , δ) : 2.25 (6H, s), 2.45 (3H, s),
 3.62 (2H, s), 4.60 (2H, d, $J=6\text{Hz}$),
 5.40-5.83 (1H, m), 6.03 (1H, d, $J=7\text{Hz}$),
 6.60 (1H, t, $J=7\text{Hz}$), 7.07-7.56 (4H, m),
 7.60 (1H, d, $J=7\text{Hz}$)

Preparation 17

Methyl iodide (3.48 g) was added dropwise to a solution of 8-(2-chlorobenzylamino)-3-dimethylaminomethyl-2-methylimidazo[1,2-a]pyridine (7.8 g) in acetone (100 ml) at room temperature and the mixture was stirred for 24 hours. The resulting precipitate was collected by filtration, washed with acetone, and dried in a desiccator to give 8-(2-chlorobenzylamino)-3-trimethylammoniomethyl-2-methylimidazo[1,2-a]pyridine iodide (11.35 g).

mp : $> 165^\circ\text{C}$ (decomp.)

IR (Nujol) : 1540, 1400, 1360, 1290 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ) : 2.50 (3H, s), 3.20 (9H, s),
 5.10 (2H, s), 5.39 (2H, s), 6.98 (2H, broad d, $J=4\text{Hz}$),
 7.30-7.86 (4H, m), 8.55 (1H, broad-t, $J=4\text{Hz}$).

Preparation 18

The following compounds were obtained according

to a similar manner to that of Preparation 17.

- (1) 8-(2-Methylbenzyloxy)-3-trimethylammoniomethyl-2-methylimidazo[1,2-a]pyridine iodide

mp : $>175^{\circ}\text{C}$ (decomp.)

IR (Nujol) : 1545, 1490, 1285, 1270 cm^{-1}

NMR (DMSO- d_6 , δ) : 2.38 (3H, s), 2.46 (3H, s),
3.13 (9H, s), 5.02 (2H, s), 5.28 (2H, s),
6.9-7.6 (6H, m), 8.45 (1H, t, $J=3.5\text{Hz}$)

- (2) 8-(1-Phenylethoxy)-3-trimethylammoniomethyl-2-methylimidazo[1,2-a]pyridine iodide

mp : 158°C (decomp.)

NMR (DMSO- d_6 , δ) : 1.63 (3H, d, $J=6\text{Hz}$),
2.49 (3H, s), 3.10 (9H, s), 4.96 (2H, s),
5.78 (1H, q, $J=6\text{Hz}$), 6.53-7.0 (2H, m),
7.11-7.65 (5H, m), 8.35 (1H, broad d, $J=6\text{Hz}$)

- (3) 8-(3-Chlorobenzyloxy)-3-trimethylammoniomethyl-2-methylimidazo[1,2-a]pyridine iodide

mp : $>153^{\circ}\text{C}$ (decomp.)

IR (Nujol) : 1540, 1290, 1080 cm^{-1}

NMR (DMSO- d_6 , δ) : 2.49 (3H, s), 3.16 (9H, s),
5.06 (2H, s), 5.39 (2H, s), 6.86-7.1 (2H, m),
7.33-7.73 (4H, m), 8.40-8.63 (1H, m)

- (4) 8-(4-Chlorobenzyloxy)-3-trimethylammoniomethyl-2-methylimidazo[1,2-a]pyridine iodide

mp : $>180^{\circ}\text{C}$ (decomp.)

NMR (DMSO- d_6 , δ) : 2.52 (2H, s), 3.22 (9H, s),
5.10 (2H, s), 5.33 (2H, s), 6.80-7.10 (2H, m),
7.30-7.70 (4H, m), 8.54 (1H, broad t, $J=3\text{Hz}$)

- (5) 8-(2-Bromobenzyloxy)-3-trimethylammoniomethyl-2-methylimidazo[1,2-a]pyridine iodide

mp : >160°C (decomp.)

NMR (DMSO-d₆, δ) : 2.47 (3H, s), 3.14 (9H, s),
5.01 (2H, s), 5.32 (2H, s), 6.86-7.06 (2H, m),
7.23-7.86 (4H, m), 8.36-8.63 (1H, m)

5

- (6) 8-(2,6-Dichlorobenzyloxy)-3-trimethylammoniomethyl-
2-methylimidazo[1,2-a]pyridine iodide

mp : 270 to 275°C (decomp.)

10

NMR (DMSO-d₆, δ) : 2.40 (3H, s), 3.10 (9H, s),
5.00 (2H, s), 5.40 (2H, s), 6.76-7.20 (2H, m),
7.40-7.70 (3H, m), 8.45 (1H, dd, J=2Hz and
6Hz)

- (7) 8-(3,4-Dichlorobenzyloxy)-3-trimethylammoniomethyl-
2-methylimidazo[1,2-a]pyridine iodide

15

mp : 190°C (decomp.)

20

NMR (DMSO-d₆, δ) : 2.43 (3H, s), 3.13 (9H, s),
5.00 (2H, s), 5.45 (2H, s), 6.46-6.76 (2H, m),
7.36-7.83 (3H, m), 8.45 (1H, dd, J=2Hz and
4Hz)

- (8) 8-(2,4-Dichlorobenzyloxy)-3-trimethylammoniomethyl-
2-methylimidazo[1,2-a]pyridine iodide

25

mp : 187°C (decomp.)

NMR (DMSO-d₆, δ) : 2.50 (3H, s), 3.20 (9H, s),
5.03 (2H, s), 5.35 (2H, s), 6.86-7.10 (2H, m),
7.50 (1H, dd, J=2Hz and 8Hz), 7.68 (1H, d,
J=2Hz), 7.75 (1H, d, J=8Hz), 8.43-8.63
(1H, m)

30

- (9) 8-Benzyloxy-3-trimethylammoniomethylimidazo[1,2-a]-
pyridine iodide

mp : 202°C (decomp.)

35

NMR (DMSO-d₆, δ) : 3.16 (9H, s), 5.10 (2H, s),
5.36 (2H, s), 6.70-7.20 (2H, m),

7.26-7.73 (5H, m), 7.86 (1H, s),
8.56 (1H, dd, J=2Hz and 6Hz)

- (10) 8-Benzyloxy-3-trimethylammoniomethyl-2-phenylimidazo[1,2-a]pyridine iodide

mp : 159°C (decomp.)

NMR (DMSO-d₆, δ) : 2.90 (9H, s), 5.23 (2H, s),
5.33 (2H, s), 6.90-7.10 (2H, m),
7.23-8.00 (10H, m), 8.56 (1H, dd, J=3Hz and
5Hz)

- (11) 8-(2-Methylbenzylamino)-3-trimethylammoniomethyl-2-methylimidazo[1,2-a]pyridine iodide

mp : 190°C (decomp.)

NMR (DMSO-d₆, δ) : 2.35 (3H, s), ca. 2.4-2.7 (3H, s),
3.12 (9H, s), 4.45 (2H, d, J=6Hz), 4.85 (2H, s),
6.08 (1H, d, J=8Hz), 6.35-6.95 (2H, m),
7.06-7.36 (4H, m), 8.03 (1H, d, J=7Hz)

- (12) 8-(2-Chlorobenzylamino)-3-trimethylammoniomethyl-2-methylimidazo[1,2-a]pyridine iodide

mp : >140°C (decomp.)

NMR (DMSO-d₆, δ) : 2.53 (3H, s), 3.16 (9H, s),
4.55 (2H, d, J=6Hz), 4.98 (2H, s), 6.03 (1H, d,
J=8Hz), 6.56-6.93 (2H, m), 7.10-7.63 (4H, m),
8.11 (1H, d, J=7Hz)

Example 1

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A solution of 2-amino-3-benzyloxy pyridine (3 g) and 3-chloro-5-hexen-2-one (2.981 g) in ethanol (15 ml) was stirred and refluxed for 45 hours and then evaporated in vacuo. To the residue was added an aqueous solution of sodium bicarbonate and the mixture was extracted with ethyl acetate. The extract was washed with water, dried over magnesium sulfate and evaporated in vacuo. The oily residue was purified by column chromatography on silica gel (50 g) using methylene chloride and then chloroform as eluents. The eluate with chloroform was evaporated in vacuo and the residual solid was recrystallized from diisopropyl ether to give 8-benzyloxy-3-allyl-2-methylimidazo[1,2-a]pyridine (0.31 g).

mp : 90.5 to 91.5°C

IR (Nujol) : 1530, 1275 cm^{-1}

NMR (CDCl_3 , δ) : 2.43 (3H, s), 3.43-3.66 (2H, m), 4.69-5.20 (2H, m), 5.30 (2H, s), ca. 5.4-6.2 (1H, m), 6.23-6.69 (2H, m), 7.13-7.58 (6H, m)

Analysis Calcd. for $\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}$:

C: 77.67; H: 6.52; N: 10.06

Found : C: 78.06; H: 6.61; N: 9.94

Example 2

A solution of 2-amino-3-benzyloxy pyridine (2 g) and 3-tosyloxy-5-hexyn-2-one (2.66 g) in ethanol (15 ml) was stirred and refluxed for 24 hours and then evaporated in vacuo. To the residue was added an aqueous solution of sodium bicarbonate and the mixture was extracted with ethyl acetate. The extract was washed with water, dried over magnesium sulfate and evaporated in vacuo. The oily residue was purified by column chromatography on silica gel (50 g) using chloroform as an eluent to give a solid, which was recrystallized from a mixture

of methylene chloride and diethyl ether to give
8-benzyloxy-3-(2-propynyl)-2-methylimidazo[1,2-a]-
pyridine (0.855 g).

mp : 112 to 112.5°C

5 IR (Nujol) : 3270, 1570, 1535, 1280, 1265, 1085,
1010 cm^{-1}

NMR (CDCl_3 , δ) : 2.05 (1H, t, $J=3\text{Hz}$), 2.48 (3H, s),
3.73 (2H, d, $J=3\text{Hz}$), 5.33 (2H, s), 6.31-6.78
(2H, m), 7.20-7.76 (6H, m)

10 Analysis Calcd. for $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}$:

C: 78.24; H: 5.84; N: 10.14

Found : C: 78.40; H: 5.72; N: 10.30

Example 3

15 8-(2-Phenylethoxy)-3-(2-propynyl)-2-methylimidazo-
[1,2-a]pyridine was obtained by reacting 2-amino-3-
(2-phenylethoxy)pyridine with 3-mesyloxy-5-hexyn-2-one
according to similar manners to those of Examples 1 and
2.

20 mp : 114 to 116°C (recrystallized from a mixture
of ethyl acetate and n-hexane)

IR (Nujol) : 3295, 3095, 2100 cm^{-1}

25 NMR (CDCl_3 , δ) : 2.07 (1H, t, $J=3\text{Hz}$), 2.49 (3H, s),
3.30 (2H, t, $J=8\text{Hz}$), 3.76 (2H, d, $J=3\text{Hz}$),
4.37 (2H, t, $J=8\text{Hz}$), 6.33-6.86 (2H, m),
7.30 (5H, s), 7.68 (1H, dd, $J=1\text{Hz}$ and 7Hz)

Analysis Calcd. for $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}$:

C: 78.59; H: 6.25; N: 9.65

Found : C: 78.43; H: 6.11; N: 9.98

Example 4

35 A solution of 2-amino-3-(2-methylbenzyloxy)pyridine
(5 g) and 3-tosyloxy-5-hexyn-2-one (7.45 g) in ethanol
(35 ml) was heated under reflux for 28 hours and then
evaporated in vacuo. The residue was dissolved in ethyl

acetate and the solution was allowed to stand at ambient temperature. The resultant precipitate was collected by filtration and dissolved in a mixture of methylene chloride and aqueous sodium bicarbonate. The organic layer was separated, washed with saturated sodium chloride aqueous solution, treated with silica gel and activated charcoal successively, and evaporated in vacuo.

The crystalline residue was recrystallized from ethyl acetate to give 8-(2-methylbenzyloxy)-3-(2-propynyl)-2-methylimidazo[1,2-a]pyridine (1.44 g).

mp : 138 to 140°C

IR (Nujol) : 3270, 1570, 1535 cm^{-1}

NMR (CDCl_3 , δ) : 2.04 (1H, t, $J=3\text{Hz}$), 2.38 (3H, s), 2.44 (3H, s), 3.75 (2H, d, $J=3\text{Hz}$), 5.28 (2H, s), 6.45 (1H, dd, $J=1\text{Hz}$ and 8Hz), 6.66 (1H, t, $J=8\text{Hz}$), 7.06-7.30 (3H, m), 7.37-7.55 (1H, m), 7.70 (1H, dd, $J=1\text{Hz}$ and 8Hz)

Analysis, Calcd. for $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}$:

C : 78.59; H : 6.25; N : 9.65

Found : C : 78.69; H : 6.11; N : 9.74

Example 5

The following compounds were prepared according to similar manners to those of Examples 1, 2, 3 and 4.

(1) 8-(2-Ethylbenzyloxy)-3-(2-propynyl)-2-methylimidazo[1,2-a]pyridine

mp : 109 to 110°C (recrystallized from a mixture of ethyl acetate and n-hexane)

IR (Nujol) : 3275 cm^{-1}

NMR (CDCl_3 , δ) : 1.24 (3H, t, $J=8\text{Hz}$), 2.03 (1H, t, $J=3\text{Hz}$), 2.43 (3H, s), 2.76 (2H, q, $J=8\text{Hz}$), 3.74 (2H, d, $J=3\text{Hz}$), 5.31 (2H, s), 6.49 (1H, d, $J=7\text{Hz}$), 6.68 (1H, t, $J=7\text{Hz}$), 7.13-7.43 (3H, m), 7.49-7.66 (1H, m), 7.81 (1H, d, $J=7\text{Hz}$)

Analysis Calcd. for $C_{20}H_{20}N_2O$:

C: 78.92; H: 6.62; N: 9.20

Found : C: 79.13; H: 6.39; N: 9.23

- 5 (2) 8-(2-Isopropylbenzyloxy)-3-(2-propynyl)-2-methylimidazo[1,2-a]pyridine

mp : 108 to 109°C (recrystallized from a mixture of ethyl acetate and n-hexane)

IR (Nujol) : 3280 cm^{-1}

10 NMR ($CDCl_3$, δ) : 1.26 (6H, d, $J=7\text{Hz}$), 2.03 (1H, t, $J=3\text{Hz}$), 2.43 (3H, s), 3.32 (1H, septet, $J=7\text{Hz}$), 3.74 (2H, d, $J=3\text{Hz}$), 5.36 (2H, s), 6.45 (1H, d, $J=7\text{Hz}$), 6.66 (1H, t, $J=7\text{Hz}$), 7.00-7.53 (4H, m), 7.69 (1H, d, $J=7\text{Hz}$)

- 15 Analysis, Calcd. for $C_{21}H_{22}N_2O$:

C: 79.21; H: 6.96; N: 8.80

Found : C: 79.32; H: 7.38; N: 8.68

- 20 (3) 8-(2-Chlorobenzyloxy)-3-(2-propynyl)-2-methylimidazo[1,2-a]pyridine

mp : 130 to 131°C (recrystallized from ethyl acetate)

IR (Nujol) : 3265, 1560, 1525 cm^{-1}

25 NMR ($CDCl_3$, δ) : 2.05 (1H, t, $J=3\text{Hz}$), 2.46 (3H, s), 3.76 (2H, d, $J=3\text{Hz}$), 5.42 (2H, s), 6.42 (1H, d, $J=7\text{Hz}$), 6.66 (1H, t, $J=7\text{Hz}$), 7.15-7.50 (3H, m), 7.53-7.70 (1H, m), 7.72 (1H, d, $J=7\text{Hz}$)

Analysis, Calcd. for $C_{18}H_{15}ClN_2O$:

C: 69.57; H: 4.86; N: 9.01

30 Found : C: 69.58; H: 5.13; N: 9.06

- (4) 8-(3-Chlorobenzyloxy)-3-(2-propynyl)-2-methylimidazo[1,2-a]pyridine.

mp : 110 to 111°C (recrystallized from a mixture of ethyl acetate and n-hexane)

35

IR (Nujol) : 3200, 1542 cm^{-1}

NMR (CDCl_3 , δ) : 2.04 (1H, t, $J=3\text{Hz}$), 2.46 (3H, s),
 3.76 (2H, d, $J=3\text{Hz}$), 5.29 (2H, s),
 6.43 (1H, d, $J=7\text{Hz}$), 6.66 (1H, t, $J=7\text{Hz}$),
 7.18-7.40 (3H, m), 7.49 (1H, s),
 7.71 (1H, d, $J=7\text{Hz}$)

Analysis Calcd. for $\text{C}_{18}\text{H}_{15}\text{ClN}_2\text{O}$:

C: 69.57; H: 4.86; N: 9.11

Found : C: 69.86; H: 4.79; N: 9.11

(5) 8-(4-Chlorobenzyloxy)-3-(2-propynyl)-2-methylimidazo-
 [1,2-a]pyridine

mp : 173 to 175°C (recrystallized from ethyl acetate)

IR (Nujol) : 3295 cm^{-1}

NMR (CDCl_3 , δ) : 2.05 (1H, t, $J=3\text{Hz}$), 2.48 (3H, s),
 3.76 (2H, d, $J=3\text{Hz}$), 5.30 (2H, s), 6.32-6.83
 (2H, m), 7.19-7.56 (4H, m), 7.72 (1H, dd,
 $J=2\text{Hz}$, 6Hz)

Analysis Calcd. for $\text{C}_{18}\text{H}_{15}\text{ClN}_2\text{O}$:

C: 69.57; H: 4.86; N: 9.01

Found : C: 69.45; H: 4.55; N: 9.18

(6) 8-(2-Bromobenzyloxy)-3-(2-propynyl)-2-
 methylimidazo[1,2-a]pyridine

mp : 156 to 157°C (recrystallized from ethyl acetate)

IR (Nujol) : 3150, 2100, 1535 cm^{-1}

NMR (CDCl_3 , δ) : 2.0-2.17 (1H, m), 2.46 (3H, s),
 3.76 (2H, d, $J=3\text{Hz}$), 5.38 (2H, s),
 6.40 (1H, d, $J=7.5\text{Hz}$), 6.65 (1H, t, $J=7.5\text{Hz}$),
 7.03-7.40 (2H, m), 7.50-7.80 (3H, m)

Analysis Calcd. for $\text{C}_{18}\text{H}_{15}\text{BrN}_2\text{O}$:

C: 60.86; H: 4.26; N: 7.89

Found : C: 61.01; H: 4.45; N: 7.84

(7) 8-(2-Fluorobenzyloxy)-3-(2-propynyl)-2-
 methylimidazo[1,2-a]pyridine

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mp : 123 to 125°C (recrystallized from a mixture
of ethyl acetate and n-hexane)

IR (Nujol) : 3300, 3275 cm^{-1}

NMR (CDCl_3 , δ) : 2.06 (1H, t, $J=3\text{Hz}$), 2.49 (3H, s),
3.77 (2H, d, $J=3\text{Hz}$), 5.40 (2H, s), 6.52 (1H, d,
 $J=7\text{Hz}$), 6.69 (1H, t, $J=7\text{Hz}$), 6.92-7.63 (4H, m),
7.73 (1H, d, $J=7\text{Hz}$)

Analysis, Calcd. for $\text{C}_{18}\text{H}_{15}\text{FN}_2\text{O}$:

C: 73.45; H: 5.14; N: 9.52

Found : C: 73.72; H: 5.02; N: 9.45

- (8) 8-(2,6-Dimethylbenzyloxy)-3-(2-propynyl)-2-methylimidazo[1,2-a]pyridine

mp : 165 to 168°C (recrystallized from a mixture
of ethanol and n-hexane)

IR (Nujol) : 3185 cm^{-1}

NMR (CDCl_3 , δ) : 2.06 (1H, t, $J=3\text{Hz}$), 2.39 and
2.40 (each s, total 9H), 3.76 (2H, d, $J=3\text{Hz}$),
5.23 (2H, s), 6.53-6.87 (2H, m), 6.94-7.28
(3H, m), 7.73 (1H, dd, $J=2\text{Hz}$ and 7Hz)

Analysis Calcd. for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}$:

C: 78.92; H: 6.62; N: 9.20

Found : C: 78.95; H: 6.38; N: 9.06

- (9) 8-(2,6-Dichlorobenzyloxy)-3-(2-propynyl)-2-methylimidazo[1,2-a]pyridine

mp : 183 to 184°C (decomp.) (recrystallized from a
mixture of methylene chloride
and diisopropyl ether)

IR (Nujol) : 3180, 1540 cm^{-1}

NMR (CDCl_3 , δ) : 2.06 (1H, t, $J=3\text{Hz}$), 2.43 (3H, s),
3.75 (2H, d, $J=3\text{Hz}$), 5.47 (2H, s),
6.57-6.89 (2H, m), 7.17-7.43 (3H, m)
7.76 (1H, dd, $J=2\text{Hz}$ and 7Hz)

Analysis Calcd. for $\text{C}_{18}\text{H}_{14}\text{Cl}_2\text{N}_2\text{O}$:

C: 62.62; H: 4.09; N: 8.11

Found : C: 63.14; H: 4.29; N: 8.17

(10) 8-(2-Naphthylmethoxy)-3-(2-propynyl)-2-methylimidazo[1,2-a]pyridine

mp : 138 to 139°C (recrystallized from a mixture of ethyl acetate and n-hexane)

IR (Nujol) : 3290 cm^{-1}

NMR (CDCl_3 , δ) : 2.04 (1H, t, $J=3\text{Hz}$), 2.50 (3H, s), 3.74 (2H, d, $J=3\text{Hz}$), 5.50 (2H, s), 6.33-6.78 (2H, m), 7.23-8.01 (8H, m)

(11) 8-(1-Naphthylmethoxy)-3-(2-propynyl)-2-methylimidazo[1,2-a]pyridine

mp : 138 to 139°C (recrystallized from a mixture of ethyl acetate and n-hexane)

IR (Nujol) : 3175, 2100 cm^{-1}

NMR (CDCl_3 , δ) : 2.05 (1H, t, $J=3\text{Hz}$), 2.46 (3H, s), 3.75 (2H, d, $J=3\text{Hz}$), 5.80 (2H, s), 6.42-6.82 (2H, m), 7.22-8.26 (8H, m)

Analysis Calcd. for $\text{C}_{22}\text{H}_{18}\text{N}_2\text{O}$:

C: 80.96; H: 5.56; N: 8.58

Found : C: 80.86; H: 5.62; N: 8.86

(12) 8-(1,2,3,4-Tetrahydro-1-naphthyloxy)-3-(2-propynyl)-2-methylimidazo[1,2-a]pyridine

mp : 139 to 141°C (recrystallized from a mixture of ethanol and n-hexane)

IR (Nujol) : 3180 cm^{-1}

NMR (CDCl_3 , δ) : 1.67-2.34 (5H, m), 2.44 (3H, s), 2.83-2.97 (2H, m), 3.78 (2H, d, $J=3\text{Hz}$), 5.79 (1H, broad t, $J=4\text{Hz}$), 6.57-6.89 (2H, m), 7.01-7.30 (3H, m), 7.36-7.54 (1H, m), 7.74 (1H, dd, $J=2\text{Hz}$ and 7Hz)

Analysis Calcd. for $\text{C}_{21}\text{H}_{20}\text{N}_2\text{O} \cdot 1/2\text{H}_2\text{O}$:

C: 77.51; H: 6.50; N: 8.61

Found : C: 78.08; H: 6.46; N: 8.66

(13) 8-(Cinnamyloxy)-3-(2-propynyl)-2-

methylimidazo[1,2-a]pyridine (trans isomer)

mp : 130 to 131°C (recrystallized from a mixture
of ethyl acetate and n-hexane)IR (Nujol) : 3280 cm^{-1} NMR (CDCl_3 , δ) : 2.04 (1H, t, $J=3\text{Hz}$), 2.44 (3H, s),
3.75 (2H, d, $J=3\text{Hz}$), 4.91 (2H, d, $J=5\text{Hz}$),
6.28-6.90 (4H, m), 7.14-7.44 (5H, m),
7.71 (1H, d, $J=7.5\text{Hz}$)Analysis Calcd. for $\text{C}_{20}\text{H}_{18}\text{N}_2\text{O}$:

C: 79.44; H: 6.00; N: 9.26

Found : C: 79.26; H: 6.10; N: 9.24

(14) 8-Cyclohexylmethoxy-3-(2-propynyl)-2-methylimidazo-
[1,2-a]pyridinemp : 118 to 119.5°C (recrystallized from a mixture
of ethyl acetate and n-hexane)IR (Nujol) : 3200, 2100 cm^{-1} NMR (CDCl_3 , δ) : 0.83-2.26 (11H, m), 2.03 (1H, t,
 $J=3\text{Hz}$), 2.46 (3H, s), 3.80 (2H, d, $J=3\text{Hz}$),
3.98 (2H, d, $J=6\text{Hz}$), 6.48 (1H, d, $J=7\text{Hz}$),
6.73 (1H, t, $J=7\text{Hz}$), 7.71 (1H, dd, $J=1\text{Hz}$ and
7Hz)Analysis Calcd. for $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}$:

C: 76.56; H: 7.85; N: 9.92

Found : C: 77.05; H: 7.54; N: 9.80

(15) 8-Ethoxy-3-(2-propynyl)-2-methylimidazo[1,2-a]-
pyridinemp : 163 to 165°C (recrystallized from a mixture
of ethyl acetate and n-hexane)IR (Nujol) : 3190, 2100 cm^{-1} NMR (CDCl_3 , δ) : 1.53 (3H, t, $J=7\text{Hz}$), 2.03 (1H, t,
 $J=3\text{Hz}$), 2.44 (3H, s), 3.73 (2H, d, $J=3\text{Hz}$),
4.20 (2H, q, $J=7\text{Hz}$), 6.40 (1H, d, $J=7\text{Hz}$),

6.66 (1H, t, J=7Hz), 7.65 (1H, dd, J=1Hz
and 7Hz)

Analysis Calcd. for $C_{13}H_{14}N_2O$:

C: 72.87; H: 6.59; N: 13.07

5 Found : C: 73.04; H: 6.48; N: 13.26

(16) 8-(2-Methylbenzyloxy)-3-(1,2-propadienyl)-2-methylimidazo[1,2-a]pyridine

10 mp : 88 to 89°C (recrystallized from a mixture
of diethyl ether and petroleum
ether)

IR (Nujol) : 1930 cm^{-1}

(17) 8-Benzyloxy-3-(2-propynyloxymethyl)-2-methylimidazo[1,2-a]pyridine hydrochloride

15 mp : 167 to 169°C

IR (Nujol) : 3180, 2560 (broad), 2125, 1675,
1580, 1090 cm^{-1}

20 (18) 8-Benzyloxy-3-(2-propynyloxymethyl)-2-methylimidazo-
[1,2-a]pyridine

mp : 103 to 104°C

IR (Nujol) : 3250, 2125, 1545, 1470, 1075 cm^{-1}

25 (19) 8-(1-Phenylethoxy)-3-(2-propynyloxymethyl)-2-methylimidazo[1,2-a]pyridine

IR (film/NaCl) : 2100 cm^{-1}

30 (20) 8-(2-Methylbenzyloxy)-3-(2-propynyloxymethyl)-2-methylimidazo[1,2-a]pyridine

mp : 87 to 89°C

IR (Nujol) : 3225, 2125, 1530, 1060, 1050 cm^{-1}

35 (21) 8-(2-Chlorobenzyloxy)-3-(2-propynyloxymethyl)-2-methylimidazo[1,2-a]pyridine

mp : 95 to 95.5°C

IR (Nujol) : 3280, 2120, 1575, 1545, 1295, 1070 cm^{-1}

(22) 8-(3-Chlorobenzyloxy)-3-(2-propynyloxymethyl)-2-methylimidazo[1,2-a]pyridine

5 mp : 81 to 83°C (recrystallized from petroleum ether)

IR (Nujol) : 3130, 2095, 1570, 1540, 1285, 1055 cm^{-1}

10 (23) 8-(4-Chlorobenzyloxy)-3-(2-propynyloxymethyl)-2-methylimidazo[1,2-a]pyridine

mp : 130 to 131°C (recrystallized from a mixture of ethyl acetate and n-hexane)

15 IR (Nujol) : 3240, 2100, 1530, 1490, 1360, 1275, 1265 cm^{-1}

(24) 8-(2-Bromobenzyloxy)-3-(2-propynyloxymethyl)-2-methylimidazo[1,2-a]pyridine

20 mp : 103 to 104°C (recrystallized from a mixture of methylene chloride and diethyl ether)

(25) 8-(2,6-Dichlorobenzyloxy)-3-(2-propynyloxymethyl)-2-methylimidazo[1,2-a]pyridine

25 mp : 129 to 130°C (recrystallized from a mixture of ethyl acetate and n-hexane)

IR (Nujol) : 3290 cm^{-1}

30 (26) 8-(3,4-Dichlorobenzyloxy)-3-(2-propynyloxymethyl)-2-methylimidazo[1,2-a]pyridine

mp : 105 to 107°C (recrystallized from a mixture of ethyl acetate and n-hexane)

IR (Nujol) : 3260, 2110, 1280, 1160 cm^{-1}

35 (27) 8-(2,4-Dichlorobenzyloxy)-3-(2-propynyloxymethyl)-2-methylimidazo[1,2-a]pyridine

mp : 123 to 124°C (recrystallized from a mixture
of ethyl acetate and n-hexane)
IR (Nujol) : 3250, 2110, 1280, 1060 cm⁻¹

(28) 8-Benzyloxy-3-(2-propynyloxymethyl)imidazo-
[1,2-a]pyridine

mp : 84 to 85°C (recrystallized from diisopropyl
ether)

IR (Nujol) : 3170, 2100 cm⁻¹

(29) 8-Benzyloxy-3-(2-propynyloxymethyl)-2-phenylimidazo-
[1,2-a]pyridine

NMR (CDCl₃, δ) : 2.40 (1H, t, J=1Hz), 4.20 (2H, d,
J=1Hz), 4.96 (2H, s), 5.33 (2H, s), 6.40-6.80
(2H, m), 7.20-7.70 (8H, m), 7.76-7.96 (3H, m)

(30) 8-(2-Methylbenzylamino)-3-(2-propynyloxymethyl)-2-
methylimidazo[1,2-a]pyridine hydrochloride

mp : 159 to 161°C (recrystallized from a mixture
of ethanol and n-hexane)

(31) 8-(2-Chlorobenzylamino)-3-(2-propynyloxymethyl)-2-
methylimidazo[1,2-a]pyridine hydrochloride

mp : 169°C (decomp.) (recrystallized from a mixture
of ethanol and diethyl ether)

(32) 8-Benzyloxy-3-allyloxymethyl-2-methylimidazo-
[1,2-a]pyridine

mp : 70 to 71°C

IR (Nujol) : 1535, 1280, 1265, 1195, 1100, 1050,
1015 cm⁻¹

(33) 8-Benzyloxy-3-(3-carboxy-2-propynyloxymethyl)-2-
methylimidazo[1,2-a]pyridine

mp : 151°C (decomp.)

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(34) 8-Benzyloxy-3-(3-ethoxycarbonyl-2-propynyloxymethyl)-
2-methylimidazo[1,2-a]pyridine

NMR (CDCl₃, δ) : 1.33 (3H, t, J=5Hz), 2.53 (3H, s),
4.20 (2H, s), 4.27 (2H, q, J=5Hz), 4.90 (2H, s),
5.30 (2H, s), 6.50 (1H, dd, J=1Hz and 5Hz),
6.65 (1H, t, J=5Hz), 7.26-7.60 (5H, m),
7.75 (1H, dd, J=1Hz and 5Hz)

Example 6

A solution of 2-amino-3-(2-methylbenzylamino)pyridine
(2 g) and 3-methoxy-5-hexyn-2-one (1.78 g) in ethanol
(40 ml) was refluxed for 31.5 hours and then evaporated
in vacuo. The residue was treated with aqueous sodium
bicarbonate solution and extracted with methylene chloride.
The extract was washed with water, dried over magnesium
sulfate, and evaporated in vacuo. The residue was
purified by column chromatography on silica gel (40 g)
with a mixture of methylene chloride and ethyl acetate
(50:1 to 10:1) as an eluent to give 8-(2-methylbenzylamino)-
3-(2-propynyl)-2-methylimidazo[1,2-a]pyridine (0.82 g).

mp : 126 to 128°C (recrystallized from diisopropyl ether)

NMR (CDCl₃, δ) : 2.04 (1H, t, J=3Hz), 2.38 (3H, s),
2.40 (3H, s), 3.73 (2H, d, J=3Hz), 4.39 (2H, d,
J=5Hz), 5.13-5.43 (1H, broad s), 6.08 (1H, d,
J=8Hz), 6.66 (1H, t, J=7Hz), 7.0-7.43 (4H, m),
7.45 (1H, d, J=6Hz)

Example 7

8-(2-Chlorobenzylamino)-3-(2-propynyl)-2-
methylimidazo[1,2-a]pyridine was obtained according to
a similar manner to that of Example 6.

mp : 115 to 116.5°C (recrystallized from a mixture
of ethyl acetate and n-hexane)

NMR (CDCl₃, δ) : 2.03 (1H, t, J=3Hz), 2.40 (3H, s),
3.68 (2H, d, J=3Hz), 4.52 (2H, d, J=6Hz),
5.55 (1H, broad t, J=6Hz), 5.95 (1H, d, J=7Hz),
6.55 (1H, t, J=7Hz), 6.96-7.55 (5H, m)

Analysis Calcd. for $C_{18}H_{16}ClN_3$:

C: 69.79; H: 5.21; N: 13.56

Found : C: 69.97; H: 5.48; N: 13.62

Example 8

Sodium bicarbonate (2.73 g) was added to a solution of 2-amino-3-(2-methylbenzyloxy)pyrazine (3.5 g) and 3-mesyloxy-5-hexyn-2-one (6.18 g) in ethanol (35 ml) and the mixture was refluxed for 12 hours. The mixture was poured into an aqueous solution of sodium bicarbonate and extracted with chloroform. The extract was washed with water, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (200 g) with a mixture of chloroform and methanol (50:1) as an eluent to give 8-(2-methylbenzyloxy)-3-(2-propynyl)-2-methylimidazo[1,2-a]pyrazine (0.182 g).

mp : 123 to 124°C

NMR ($CDCl_3$, δ) : 2.08 (1H, t, $J=3Hz$), 2.42 (3H, s),
2.45 (3H, s), 3.72 (2H, d, $J=3Hz$), 5.55
(2H, s), 7.00-7.55 (4H, m), 7.35 (1H, d, $J=5Hz$),
7.63 (1H, d, $J=5Hz$)

Example 9

8-(2-Methylbenzylamino)-3-(2-propynyl)-2-methylimidazo[1,2-a]pyrazine hydrochloride was obtained according to a similar manner to that of Example 8.

mp : 184 to 186°C (decomp.)

Analysis Calcd. for $C_{18}H_{18}N_4 \cdot HCl$:

C: 66.19; H: 5.95; N: 17.38; Cl: 10.90

Found : C: 66.15; H: 5.86; N: 17.14; Cl: 10.52

IR (Nujol) : 3350, 3180, 2560, 1660, 1635, 1525 cm^{-1}

NMR ($DMSO-d_6$, δ) : 2.37 (3H, s), ca. 2.3-2.7 (3H, s),
3.13 (1H, t, $J=3Hz$), 4.08 (2H, d, $J=3Hz$),
4.90 (2H, d, $J=6Hz$), 7.00-7.50 (4H, m),
7.42 (1H, d, $J=5Hz$), 7.92 (1H, d, $J=5Hz$),
9.70-10.2 (1H, broad)

Example 10

A solution of 8-(2-methylbenzyloxy)-3-(2-propynyl)-2-methylimidazo[1,2-a]pyridine (0.99 g) and 1N-sodium hydroxide solution (5.65 ml) in methanol (50 ml) was stirred for 72 hours at room temperature. The mixture was evaporated in vacuo and the residue was dissolved in chloroform. The solution was washed with brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (14 g) with a mixture of chloroform and ethyl acetate (15:1) as an eluent to give 8-(2-methylbenzyloxy)-3-(1,2-propadienyl)-2-methylimidazo[1,2-a]pyridine (0.27 g).

mp : 88 to 89°C (recrystallized from a mixture of diethyl ether and petroleum ether).

IR (Nujol) : 1930 cm^{-1}

NMR (CDCl_3 , δ) : 2.40 (3H, s), 2.46 (3H, s), 5.26 (2H, s), 5.26-5.43 (2H, m), 6.40-6.76 (3H, m), 7.06-7.30 (3H, m), 7.33-7.53 (1H, m), 8.10 (1H, dd, $J=1\text{Hz}$ and 7Hz)

Analysis Calcd. for $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}$:

C: 78.59; H: 6.25; N: 9.65

Found : C: 78.86; H: 6.02; N: 9.57

Example 11

To a solution of sodium hydride (61% in mineral oil dispersion) (7.39 g) in 2-propynyl alcohol (300 ml) was added 8-benzyloxy-3-trimethylammoniomethyl-2-methylimidazo[1,2-a]pyridine iodide (74.6 g), and the mixture was heated at 90-95°C with stirring for 2.5 hours. After being cooled, the mixture was evaporated in vacuo and the residue was dissolved in methylene chloride. The solution was washed with water, dried over magnesium sulfate, and evaporated in vacuo. The oily residue was purified by column chromatography on

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silic gel (200 g) with methylene chloride as an eluent and the fractions containing the object compound were combined. The resultant solution was treated with a solution of hydrogen chloride in ethanol to give 8-benzyloxy-3-(2-propynyloxymethyl)-2-methylimidazo[1,2-a]-pyridine hydrochloride (37.5 g).

mp : 167 to 169°C

IR (Nujol) : 3180, 2560 (broad), 2125, 1675, 1580,
1090 cm^{-1}

NMR (D_2O , δ) : 2.56 (3H, s), 3.03 (1H, t, $J=2\text{Hz}$),
4.31 (2H, d, $J=2\text{Hz}$), 4.96 (2H, s), 5.29 (2H, s),
7.13-7.56 (7H, m), 8.01-8.14 (1H, m)

Analysis Calcd. for $\text{C}_{19}\text{H}_{19}\text{ClN}_2\text{O}_2$:

C: 66.57; H: 5.59; N: 8.17

Found : C: 66.37; H: 5.33; N: 8.06

Example 12

A solution of 8-benzyloxy-3-(2-propynyloxymethyl)-2-methylimidazo[1,2-a]pyridine hydrochloride (35.5 g) in hot water (700 ml) was neutralized with aqueous sodium hydroxide solution and extracted with methylene chloride. The extract was washed with water, dried over magnesium sulfate, treated with activated charcoal, and evaporated in vacuo. The residual solid was recrystallized from a mixture of methylene chloride and n-hexane to give 8-benzyloxy-3-(2-propynyloxymethyl)-2-methylimidazo[1,2-a]pyridine (26.03 g).

mp : 103 to 104°C

IR (Nujol) : 3250, 2125, 1545, 1470, 1075 cm^{-1}

NMR (CDCl_3 , δ) : 2.43-2.60 (1H, m), 2.53 (3H, s),
4.07 (2H, d, $J=2\text{Hz}$), 4.87 (2H, s), 5.33 (2H, s),
6.33-6.76 (2H, m), 7.20-7.60 (5H, m),
7.73 (1H, dd, $J=2\text{Hz}$ and 6Hz)

Example 13

To a solution of sodium hydride (63.6% in mineral oil dispersion, 0.285 g) in 2-propynyl alcohol (12 ml) was added 8-(2-methylbenzyloxy)-3-trimethylammoniomethyl-
 5 2-methylimidazo[1,2-a]pyridine iodide (3 g) and the mixture was heated at 85-100°C for 1.5 hours. After being cooled, the mixture was poured into ice-water and the resulting precipitate was collected by filtration and dissolved in methylene chloride. The solution was treated successively
 10 with silica gel (4.5 g) and activated charcoal and evaporated in vacuo. The crystalline residue was recrystallized from a mixture of ethyl acetate and petroleum ether to give 8-(2-methylbenzyloxy)-3-(2-propynyloxymethyl)-2-methylimidazo[1,2-a]pyridine (1.18 g).

15 mp : 87 to 89°C

IR (Nujol) : 3225, 2125, 1530, 1060, 1050 cm^{-1}

NMR (CDCl_3 , δ) : ca. 2.3-2.6 (1H), 2.40 (3H, s),

2.50 (3H, s), 4.06 (2H, d, $J=2\text{Hz}$), 4.86

(2H, s), 5.29 (2H, s), 6.32-6.8 (2H, m),

20 7.0-7.56 (4H, m), 7.75 (1H, dd, $J=2\text{Hz}$, 5Hz),

Analysis Calcd. for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_2$:

C: 74.98; H: 6.29; N: 8.74

Found : C: 74.98; H: 6.05; N: 8.71

Example 14

To a solution of sodium hydride (60% in mineral oil dispersion, 0.186 g) in 2-propynyl alcohol (8 ml) was added 8-(2-chlorobenzyloxy)-3-trimethylammonio-
 30 methyl-2-methylimidazo[1,2-a]pyridine iodide (2 g) and the mixture was heated at 90-95°C with stirring for 1 hour. After being cooled, the mixture was poured into ice-water and the resulting precipitate was collected by filtration and dissolved in methylene
 35 chloride. The solution was treated successively with silica gel (1 g) and activated charcoal and evaporated

in vacuo. The crystalline residue was recrystallized from a mixture of methylene chloride and n-hexane to give 8-(2-chlorobenzyloxy)-3-(2-propynyloxymethyl)-2-methylimidazo[1,2-a]pyridine (0.9 g).

5 mp : 95 to 95.5°C
 IR (Nujol) : 3280, 2120, 1575, 1545, 1295,
 1070 cm^{-1}
 NMR (CDCl_3 , δ) : ca. 2.4-2.7 (1H), 2.58 (3H, s),
 4.13 (2H, d, $J=2\text{Hz}$), 4.94 (2H, s), 5.47
 10 (2H, s), 6.39-6.85 (2H, m), 7.10-7.50 (3H, m),
 7.50-7.92 (2H, m)
 Analysis Calcd. for $\text{C}_{19}\text{H}_{17}\text{ClN}_2\text{O}_2$:
 C: 66.96; H: 5.03; N: 8.22
 Found : C: 67.13; H: 4.93; N: 8.12

15

Example 15

The following compounds were obtained according to similar manners to those of Examples 11, 13 and 14.

20 (1) 8-(1-Phenylethoxy)-3-(2-propynyloxymethyl)-2-methylimidazo[1,2-a]pyridine
 IR (film/ NaCl) : 2100 cm^{-1}
 NMR (CDCl_3 , δ) : 1.80 (3H, d, $J=6\text{Hz}$), 2.40-2.60
 (1H, m), 2.53 (3H, s), 4.05 (2H, d, $J=2\text{Hz}$),
 25 4.85 (2H, s), 5.52 (1H, q, $J=6\text{Hz}$), 6.16-6.69
 (2H, m), 7.11-7.56 (5H, m), 7.64 (1H, dd,
 $J=1\text{Hz}$ and 6Hz)
 (2) 8-(3-Chlorobenzyloxy)-3-(2-propynyloxymethyl)-2-methylimidazo[1,2-a]pyridine
 30 mp : 81 to 83°C (recrystallized from petroleum ether)
 IR (Nujol) : 3130, 2095, 1570, 1540, 1285, 1055 cm^{-1}
 NMR (CDCl_3 , δ) : 2.43-2.60 (1H, m), 4.52 (3H, s),
 35 4.08 (2H, d, $J=2\text{Hz}$), 4.88 (2H, s), 5.29 (2H, s),

6.32-6.80 (2H, m), 7.10-7.6 (4H, m),

7.75 (1H, dd, J=2Hz and 7Hz)

Analysis Calcd. for $C_{19}H_{17}ClN_2O_2$:

C: 66.96; H: 5.03; N: 8.22

Found C: 67.23; H: 4.88; N: 8.15

(3) 8-(4-Chlorobenzyloxy)-3-(2-propynyloxymethyl)-2-methylimidazo[1,2-a]pyridine

mp : 130 to 131°C (recrystallized from a mixture of ethyl acetate and n-hexane)

IR (Nujol) : 3240, 2100, 1530, 1490, 1360, 1275, 1265 cm^{-1}

NMR ($CDCl_3$, δ) : 2.38-2.58 (1H, m), 2.52 (3H, s), 4.06 (2H, d, J=2Hz), 4.86 (2H, s), 5.26 (2H, s), 6.26-6.73 (2H, m), 7.13-7.56 (4H, m), 7.76 (1H, dd, J=2Hz and 7Hz)

Analysis Calcd. for $C_{19}H_{17}ClN_2O_2$:

C: 66.96; H: 5.03; N: 8.22

Found : C: 66.91; H: 4.95; N: 8.08

(4) 8-(2-Bromobenzyloxy)-3-(2-propynyloxymethyl)-2-methylimidazo[1,2-a]pyridine

mp : 103 to 104°C (recrystallized from a mixture of methylene chloride and diethyl ether)

NMR ($CDCl_3$, δ) : 2.43-2.63 (1H, m), 2.52 (3H, s), 4.08 (2H, d, J=2Hz), 4.88 (2H, s), 5.39 (2H, s), 6.33-6.81 (2H, m), 7.06-7.73 (4H, m), 7.75 (1H, dd, J=2Hz and 7Hz)

(5) 8-(2,6-Dichlorobenzyloxy)-3-(2-propynyloxymethyl)-2-methylimidazo[1,2-a]pyridine

mp : 129 to 130°C (recrystallized from a mixture of ethyl acetate and n-hexane)

IR (Nujol) : 3290 cm^{-1}

NMR (CDCl_3 , δ) : 2.45-2.60 (1H, m), 2.46 (3H, s),
4.06 (2H, d, $J=2\text{Hz}$), 4.86 (2H, s), 5.43 (2H, s),
6.60-6.85 (2H, m), 7.06-7.45 (3H, m), 7.80
(1H, dd, $J=2\text{Hz}$ and 3Hz)

Analysis Calcd. for $\text{C}_{19}\text{H}_{16}\text{Cl}_2\text{N}_2\text{O}_2$:
C: 60.81; H: 4.30; N: 7.47
Found : C: 61.31; H: 4.33; N: 7.48

10 (6) 8-(3,4-Dichlorobenzyloxy)-3-(2-propynyloxymethyl)-
2-methylimidazo[1,2-a]pyridine

mp : 105 to 107°C (recrystallized from a mixture
of ethyl acetate and n-hexane)

IR (Nujol) : 3260 , 2110 , 1280 , 1160 cm^{-1}

15 NMR (CDCl_3 , δ) : 2.40-2.60 (1H, m), 2.46 (3H, s),
4.05 (2H, d, $J=2\text{Hz}$), 4.83 (2H, s), 5.23 (2H, s),
6.26-6.80 (2H, m), 7.13-7.63 (3H, m),
7.75 (1H, dd, $J=1\text{Hz}$ and 7Hz)

Analysis Calcd. for $\text{C}_{19}\text{H}_{16}\text{Cl}_2\text{N}_2\text{O}_2$:
C: 60.81; H: 4.30; N: 7.47
Found : C: 61.26; H: 4.23; N: 7.55

(7) 8-(2,4-Dichlorobenzyloxy)-3-(2-propynyloxymethyl)-
2-methylimidazo[1,2-a]pyridine

25 mp : 123 to 124°C (recrystallized from a mixture
of ethyl acetate and n-hexane)

IR (Nujol) : 3250 , 2110 , 1280 , 1060 cm^{-1}

30 NMR (CDCl_3 , δ) : 2.40-2.66 (1H, m), 2.50 (3H, s)
4.08 (2H, d, $J=2\text{Hz}$), 4.90 (2H, s), 5.36 (2H, s),
6.30-6.83 (2H, m), 7.20 (1H, dd, $J=2\text{Hz}$ and 8Hz),
7.40 (1H, d, $J=2\text{Hz}$), 7.50 (1H, d, $J=8\text{Hz}$),
7.80 (1H, dd, $J=1\text{Hz}$ and 7Hz)

35 Analysis Calcd. for $\text{C}_{19}\text{H}_{16}\text{Cl}_2\text{N}_2\text{O}_2$:
C: 60.81; H: 4.30; N: 7.47
Found : C: 61.29; H: 4.25; N: 7.41

- (8) 8-Benzyloxy-3-(2-propynyloxymethyl)imidazo[1,2-a]-pyridine

mp : 84 to 85°C (recrystallized from diisopropyl ether)

IR (Nujol) : 3170, 2100 cm^{-1}

NMR (CDCl_3 , δ) : 2.46 (1H, t, $J=2\text{Hz}$), 4.13 (2H, d, $J=2\text{Hz}$), 4.9 (2H, s), 5.33 (2H, s), 6.40-6.90 (2H, m), 7.23-7.60 (5H, m), 7.60 (1H, s), 7.83 (1H, dd, $J=2\text{Hz}$ and 7Hz)

Analysis Calcd. for $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_2$:

C: 73.95; H: 5.52; N: 9.58

Found : C: 73.74; H: 5.30; N: 9.47

- (9) 8-Benzyloxy-3-(2-propynyloxymethyl)-2-phenylimidazo[1,2-a]pyridine

NMR (CDCl_3 , δ) : 2.40 (1H, t, $J=1\text{Hz}$), 4.20 (2H, d, $J=1\text{Hz}$), 4.96 (2H, s), 5.33 (2H, s), 6.40-6.80 (2H, m), 7.20-7.70 (8H, m), 7.76-7.96 (3H, m)

- (10) 8-(2-Methylbenzylamino)-3-(2-propynyloxymethyl)-2-methylimidazo[1,2-a]pyridine hydrochloride

mp : 159 to 161°C (recrystallized from a mixture of ethanol and n-hexane)

NMR ($\text{DMSO}-d_6$, δ) : 2.39 (3H, s), ca. 2.4-2.7 (3H, s), 3.50 (1H, t, $J=2\text{Hz}$), 4.39 (2H, d, $J=2\text{Hz}$), 4.50 (2H, broad d, $J=5\text{Hz}$), 4.91 (2H, s), 6.73 (1H, d, $J=8\text{Hz}$), 7.06-7.80 (6H, m), 7.91 (1H, d, $J=6\text{Hz}$)

Analysis Calcd. for $\text{C}_{20}\text{H}_{22}\text{ClN}_3\text{O}$:

C: 67.50; H: 6.23; N: 11.81

Found : C: 67.87; H: 6.43; N: 11.87

- (11) 8-(2-Chlorobenzylamino)-3-(2-propynyloxymethyl)-2-methylimidazo[1,2-a]pyridine hydrochloride

mp : 169°C (decomp.) (crystallized from a mixture
of ethanol and diethyl ether)

NMR (DMSO- d_6 , δ) : 2.56 (3H, s), 3.52 (1H, t,
J=2Hz), 4.25 (2H, d, J=2Hz), 4.85 (2H, broad s),
4.95 (2H, s), 6.73 (1H, d, J=8Hz), 7.13-8.13
(7H, m)

Analysis Calcd. for $C_{19}H_{19}Cl_2N_3O$:

C: 60.65; H: 5.09; N: 11.17

Found : C: 60.71; H: 5.39; N: 10.98

(12) 8-Benzyloxy-3-allyloxymethyl-2-methylimidazo-
[1,2-a]pyridine

mp : 70 to 71°C

IR (Nujol) : 1535, 1280, 1265, 1195, 1100, 1050,
1015 cm^{-1}

NMR (CDCl₃, δ) : 2.50 (3H, s), 3.95 (2H, d, J=6Hz),
4.76 (2H, s), 5.0-5.5 (2H, m), 5.33 (2H, s),
5.6-6.3 (1H, m), 6.36-6.79 (2H, m),
7.20-7.62 (5H, m), 7.75 (1H, dd, J=2Hz and
6Hz)

Analysis Calcd. for $C_{19}H_{20}N_2O_2$:

C: 74.00; H: 6.54; N: 9.08

Found : C: 74.35; H: 6.48; N: 9.04

(13) 8-Benzyloxy-3-(3-carboxy-2-propynyloxymethyl)-2-
methylimidazo[1,2-a]pyridine

mp : 151°C (decomp.)

(14) 8-Benzyloxy-3-(3-ethoxycarbonyl-2-propynyloxymethyl)-
2-methylimidazo[1,2-a]pyridine

NMR (CDCl₃, δ) : 1.33 (3H, t, J=5Hz), 2.53 (3H, s),
4.20 (2H, s), 4.27 (2H, q, J=5Hz), 4.90 (2H, s),
5.30 (2H, s), 6.50 (1H, dd, J=1Hz and 5Hz),
6.65 (1H, t, J=5Hz), 7.26-7.60 (5H, m),
7.75 (1H, dd, J=1Hz and 5Hz)

Example 16

To a solution of 8-benzyloxy-3-(2-propynyloxymethyl)-
 2-methylimidazo[1,2-a]pyridine (1 g) in tetrahydrofuran
 (10 ml) was added dropwise 10% solution of n-butyllithium
 in n-hexane (2.09 ml) at -60°C under a nitrogen
 atmosphere. After being stirred for 10 minutes the
 solution was treated with dry ice (1.4 g), allowed to
 warm to room temperature, and acidified with diluted
 acetic acid. The resulting precipitates were collected
 by filtration, washed with water, and recrystallized
 from methanol to give 8-benzyloxy-3-(3-carboxy-2-
 propynyloxymethyl)-2-methylimidazo[1,2-a]pyridine
 (0.67 g).

mp : 151°C (decomp.)

NMR (DMSO-d₆, δ) : 2.36 (3H, s), 4.30 (2H, s),
 4.85 (2H, s), 5.26 (2H, s), 5.93 (1H, broad s),
 6.80-7.03 (2H, m), 7.26-7.63 (5H, m),
 7.86-8.10 (1H, m)

Analysis Calcd. for C₂₀H₁₈N₂O₄ :

C: 65.04; H: 5.72; N: 7.36

Found : C: 65.07; H: 5.54; N: 7.35

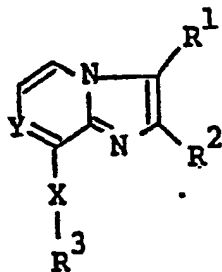
Example 17

8-Benzyloxy-3-(3-ethoxycarbonyl-2-propynyloxymethyl)-
 2-methylimidazo[1,2-a]pyridine was obtained by reacting
 8-benzyloxy-3-(2-propynyloxymethyl)-2-methylimidazo-
 [1,2-a]pyridine with ethyl chloroformate according to
 a similar manner to that of Example 16.

NMR (CDCl₃, δ) : 1.33 (3H, t, J=5Hz), 2.53 (3H, s),
 4.20 (2H, s), 4.27 (2H, q, J=5Hz), 4.90 (2H, s),
 5.30 (2H, s), 6.50 (1H, dd, J=1Hz and 5Hz),
 6.65 (1H, t, J=5Hz), 7.26-7.60 (5H, m),
 7.75 (1H, dd, J=1Hz and 5Hz)

What we claim is :

1. Imidazoheterocyclic compounds of the formula:



wherein R^1 is lower alkenyl, lower alkynyl,
lower alkadienyl,
lower alkenyloxy(lower)alkyl,
lower alkynyloxy(lower)alkyl,
carboxy(lower)alkynyloxy(lower)alkyl or
protected carboxy(lower)alkynyloxy-
(lower)alkyl,
 R^2 is hydrogen, lower alkyl or aryl,
 R^3 is ar(lower)alkyl which may have one or more
suitable substituent(s),
ar(lower)alkenyl, condensed bicyclic
hydrocarbon group, lower alkyl having
cyclo(lower)alkyl or lower alkyl,
X is O or NH, and
Y is CH or N

and a pharmaceutical acceptable salt thereof.

2. A compound of claim 1, wherein

R^1 is lower alkenyl, lower alkynyl, lower alkadienyl,
lower alkenyloxy(lower)alkyl,
lower alkynyloxy(lower)alkyl,
carboxy(lower)alkynyloxy(lower)alkyl or
esterified carboxy(lower)alkynyloxy(lower)alkyl.

3. A compound of claim 2, wherein

R^1 is lower alkenyl, lower alkynyl, lower alkadienyl, lower alkenyloxy(lower)alkyl, lower alkynyloxy(lower)alkyl, carboxy(lower)alkynyloxy(lower)alkyl or (lower)alkoxycarbonyl(lower)alkynyloxy(lower)-alkyl and

R^3 is ar(lower)alkyl which may have one or more suitable substituent(s), ar(lower)alkenyl, benzene-condensed cyclo(lower)alkyl, lower alkyl having cyclo(lower)alkyl or lower alkyl.

4. A compound of claim 3, wherein

Y is CH.

5. A compound of claim 4, wherein

R^3 is ar(lower)alkyl which may have one or more suitable substituent(s) selected from a group consisting of lower alkyl and halogen.

6. A compound of claim 5, wherein

R^3 is phenyl(lower)alkyl or naphthyl(lower)alkyl, each of which may have 1 to 3 suitable substituent(s) selected from a group consisting of lower alkyl and halogen.

7. A compound of claim 6, wherein

R^1 is allyl, 2-propynyl, 1,2-propadienyl, allyloxymethyl, 2-propynyloxymethyl, 3-carboxy-2-propynyloxymethyl or 3-ethoxycarbonyl-2-propynyloxymethyl,

R^2 is hydrogen, methyl or phenyl, and

R^3 is benzyl which may have 1 or 2 suitable substituent(s) selected from a group consisting of methyl, ethyl, isopropyl, fluoro, chloro and bromo, 1-phenylethyl, 2-phenylethyl, 1-naphthylmethyl or 2-naphthylmethyl.

8. A compound of claim 7, which is selected from a group consisting of:

8-benzyloxy-3-allyl-2-methylimidazo[1,2-a]pyridine,
8-benzyloxy-3-(2-propynyl)-2-methylimidazo[1,2-a]pyridine,
8-(2-phenylethoxy)-3-(2-propynyl)-2-methylimidazo[1,2-a]-pyridine,
8-(2-methylbenzyloxy)-3-(2-propynyl)-2-methylimidazo[1,2-a]-pyridine,
8-(2-ethylbenzyloxy)-3-(2-propynyl)-2-methylimidazo[1,2-a]-pyridine,
8-(2-isopropylbenzyloxy)-3-(2-propynyl)-2-methylimidazo-[1,2-a]pyridine,
8-(2-chlorobenzyloxy)-3-(2-propynyl)-2-methylimidazo[1,2-a]-pyridine,
8-(3-chlorobenzyloxy)-3-(2-propynyl)-2-methylimidazo[1,2-a]-pyridine,
8-(4-chlorobenzyloxy)-3-(2-propynyl)-2-methylimidazo[1,2-a]-pyridine,
8-(2-bromobenzyloxy)-3-(2-propynyl)-2-methylimidazo[1,2-a]-pyridine,
8-(2-fluorobenzyloxy)-3-(2-propynyl)-2-methylimidazo-[1,2-a]pyridine,
8-(2,6-dimethylbenzyloxy)-3-(2-propynyl)-2-methylimidazo-[1,2-a]pyridine,
8-(2,6-dichlorobenzyloxy)-3-(2-propynyl)-2-methylimidazo-[1,2-a]pyridine,

8-(2-naphthylmethoxy)-3-(2-propynyl)-2-methylimidazo-
[1,2-a]pyridine,
8-(1-naphthylmethoxy)-3-(2-propynyl)-2-methylimidazo-
[1,2-a]pyridine,
5 8-(2-methylbenzylamino)-3-(2-propynyl)-2-methylimidazo-
[1,2-a]pyridine,
8-(2-chlorobenzylamino)-3-(2-propynyl)-2-methylimidazo-
[1,2-a]pyridine,
0 8-(2-methylbenzyloxy)-3-(1,2-propadienyl)-2-methylimidazo-
[1,2-a]pyridine,
8-benzyloxy-3-(2-propynyloxymethyl)-2-methylimidazo[1,2-a]-
pyridine hydrochloride,
8-benzyloxy-3-(2-propynyloxymethyl)-2-methylimidazo[1,2-a]-
pyridine,
5 8-(1-phenylethoxy)-3-(2-propynyloxymethyl)-2-methylimidazo-
[1,2-a]pyridine,
8-(2-methylbenzyloxy)-3-(2-propynyloxymethyl)-2-
methylimidazo[1,2-a]pyridine,
8-(2-chlorobenzyloxy)-3-(2-propynyloxymethyl)-2-
methylimidazo[1,2-a]pyridine,
8-(3-chlorobenzyloxy)-3-(2-propynyloxymethyl)-2-
methylimidazo[1,2-a]pyridine,
8-(4-chlorobenzyloxy)-3-(2-propynyloxymethyl)-2-
methylimidazo[1,2-a]pyridine,
8-(2-bromobenzyloxy)-3-(2-propynyloxymethyl)-2-
methylimidazo[1,2-a]pyridine,
8-(2,6-dichlorobenzyloxy)-3-(2-propynyloxymethyl)-2-
methylimidazo[1,2-a]pyridine,
8-(3,4-dichlorobenzyloxy)-3-(2-propynyloxymethyl)-2-
methylimidazo[1,2-a]pyridine,
8-(2,4-dichlorobenzyloxy)-3-(2-propynyloxymethyl)-2-
methylimidazo[1,2-a]pyridine,
8-benzyloxy-3-(2-propynyloxymethyl)imidazo[1,2-a]pyridine,

8-benzyloxy-3-(2-propynyloxymethyl)-2-phenylimidazo[1,2-a]-pyridine,
8-(2-methylbenzylamino)-3-(2-propynyloxymethyl)-2-methylimidazo[1,2-a]pyridine hydrochloride,
8-(2-chlorobenzylamino)-3-(2-propynyloxymethyl)-2-methylimidazo[1,2-a]pyridine hydrochloride,
8-benzyloxy-3-allyloxymethyl-2-methylimidazo[1,2-a]pyridine,
8-benzyloxy-3-(3-carboxy-2-propynyloxymethyl)-2-methylimidazo[1,2-a]pyridine, and
8-benzyloxy-3-(3-ethoxycarbonyl-2-propynyloxymethyl)-2-methylimidazo[1,2-a]pyridine.

9. A compound of claim 8, which is
8-(2-chlorobenzyloxy)-3-(2-propynyloxymethyl)-2-methylimidazo[1,2-a]pyridine.

10. A compound of claim 4, wherein
R¹ is lower alkynyl,
R² is lower alkyl,
R³ is phenyl(lower)alkenyl, 1,2,3,4-tetrahydronaphthyl,
lower alkyl having cyclo(lower)alkyl or lower
alkyl, and
X is O.

11. A compound of claim 10, wherein
R¹ is 2-propynyl,
R² is methyl, and
R³ is cinnamyl, 1,2,3,4-tetrahydro-1-naphthyl,
cyclohexylmethyl or ethyl.

12. A compound of claim 11, which is selected from a group consisting of:

8-(cinnamyloxy)-3-(2-propynyl)-2-methylimidazo[1,2-a]-pyridine,

8-(1,2,3,4-tetrahydro-1-naphthyloxy)-3-(2-propynyl)-2-methylimidazo[1,2-a]pyridine,

8-cyclohexylmethoxy-3-(2-propynyl)-2-methylimidazo[1,2-a]-pyridine, and

8-ethoxy-3-(2-propynyl)-2-methylimidazo[1,2-a]pyridine.

13. A compound of claim 3, wherein

Y is N.

14. A compound of claim 13, wherein

R¹ is lower alkynyl,

R² is lower alkyl, and

R³ is phenyl(lower)alkyl which may have lower alkyl.

15. A compound of claim 14, wherein

R¹ is 2-propynyl,

R² is methyl, and

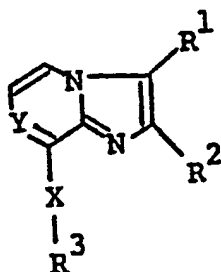
R³ is benzyl which may have methyl.

16. A compound of claim 15, which is selected from a group consisting of:

8-(2-methylbenzyloxy)-3-(2-propynyl)-2-methylimidazo[1,2-a]-pyrazine, and

8-(2-methylbenzylamino)-3-(2-propynyl)-2-methylimidazo-[1,2-a]pyrazine.

17. A process for preparing imidazoheterocyclic compounds of the formula:



wherein R^1 is lower alkenyl, lower alkynyl, lower alkadienyl, lower alkenyloxy(lower)alkyl, lower alkynyloxy(lower)alkyl, carboxy(lower)alkynyloxy(lower)alkyl or protected carboxy(lower)alkynyloxy(lower)alkyl,

R^2 is hydrogen, lower alkyl or aryl,

R^3 is ar(lower)alkyl which may have one or more suitable substituent(s), ar(lower)alkenyl, condensed bicyclic hydrocarbon group, lower alkyl having cyclo(lower)alkyl or lower alkyl,

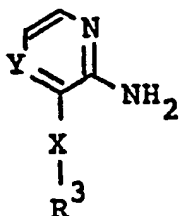
X is O or NH, and

Y is CH or N,

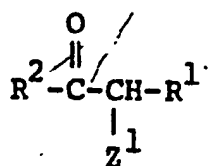
or a salt thereof,

which comprises

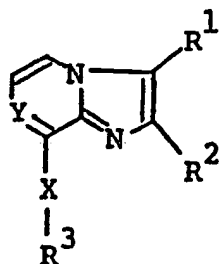
- (1) reacting a compound of the formula:



wherein R^3 , X and Y are each as defined above,
or a salt thereof, with a compound of the formula:

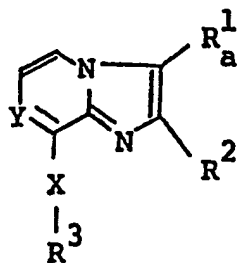


wherein R^1 and R^2 are each as defined above, and
 Z^1 is an acid residue,
or a salt thereof, to give a compound of the formula:

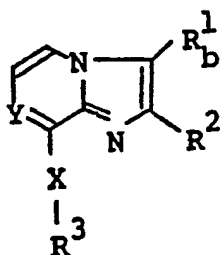


wherein R^1 , R^2 , R^3 , X and Y are each as defined above,
or a salt thereof, and

(2) subjecting a compound of the formula:

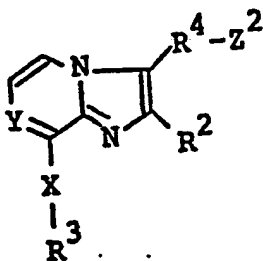


wherein R^2 , R^3 , X and Y are each as defined above, and
 R_a^1 is lower alkynyl,
or a salt thereof, to isomerization reaction, to give a
compound of the formula:



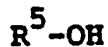
wherein R^2 , R^3 , X and Y are each as defined above, and
 R_b^1 is cumulated lower alkadienyl,
 or a salt thereof, and

(3) reacting a compound of the formula:



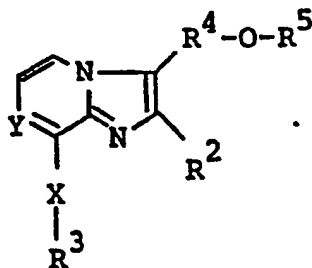
wherein R^2 , R^3 , X and Y are each as defined above,
 R^4 is lower alkylene, and
 Z^2 is a leaving group,

or a salt thereof, with a compound of the formula:



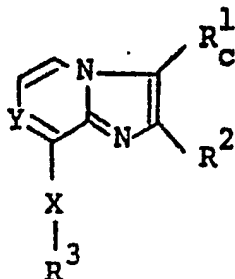
wherein R^5 is lower alkenyl, lower alkynyl,
 carboxy(lower)alkynyl or protected
 carboxy(lower)alkynyl,

or a salt thereof, to give a compound of the formula:

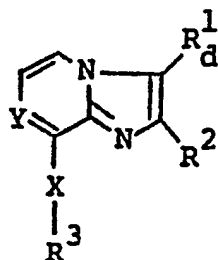


wherein R^2 , R^3 , R^4 , R^5 , X and Y are each as defined above,
or a salt thereof, and

(4) subjecting a compound of the formula:



wherein R^2 , R^3 , X and Y are each as defined above, and
 R_c^1 is (ω -lower alkynyloxy) (lower)alkyl,
or a salt thereof, to acylation reaction, to give a
compound of the formula:



wherein R^2 , R^3 , X and Y are each as defined above, and
 R_d^1 is (ω -carboxy- ω -lower alkynyloxy)-
(lower)alkyl or
(ω -protected carboxy- ω -lower
alkynyloxy) (lower)alkyl,
or a salt thereof.

18. A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers.
19. Use of compounds of claim 1 or pharmaceutically acceptable salts thereof as a medicament.
20. Use of compounds of claim 1 or pharmaceutically acceptable salts thereof in treating ulcer.
21. Use of compounds of claim 1 or pharmaceutically acceptable salts thereof for manufacture of medicament for treating ulcer.



DOCUMENTS CONSIDERED TO BE RELEVANT			EP 86107418.5
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
A	US - A - 4 450 164 (BRISTOL) * Claims 1,40; column 5 * --	1-12, 17,18, 21	C 07 D 471/04 C 07 D 487/04 A 61 K 31/44 A 61 K 31/495
A	US - A - 4 507 294 (BRISTOL) * Claims 1,18; columns 7,8 * --	1-3, 13-18, 21	(C 07 D 471/04 C 07 D 221:00 C 07 D 235/00) (C 07 D 487/04
A	EP - A1 - 0 033 094 (SCHERING CORPORATION) * Claims 1,8-10; abstract * ----	1-12, 17,18, 21	C 07 D 241:00 C 07 D 235:00)
			TECHNICAL FIELDS SEARCHED (Int. Cl. 4)
			C 07 D 471/00 C 07 D 487/00
INCOMPLETE SEARCH			
<p>The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.</p> <p>Claims searched completely: 1-18, 21 Claims searched incompletely: - Claims not searched: 19, 20 Reason for the limitation of the search:</p> <p>(Method for treatment of the human or animal body by therapy (Article 52(4) EPC)</p>			
Place of search VIENNA		Date of completion of the search 10-09-1986	Examiner ORDER
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	